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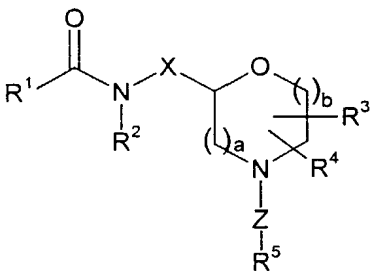
(54) Title: MORPHOLIN-ACETAMIDE DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISEASES



(I)

(57) Abstract: Compounds of formula (I) wherein: R^1 represents C_{1-16} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{2-6}alkynyl-Y^1-, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-16} alkyl-SO_2-Y^1-,M-Y^1-,J^2-Y^1-, -CN or C_{3-8} cycloalkyl-Y^1-or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-16} Alkyl groups; R^2 represents hydrogen or C_{1-16} alkyl; X represents ethylene or a group of formula CR^eR^f wherein R^e and R^f independently represent hydrogen or C^{1-14} alkyl or R^e and R^f may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group; R^3 and R^4 independently represent hydrogen or C_{1-14} alkyl; Z represents a bond, CO, SO_2, $CR^9R^6(CH_2)_n$, $(CH_2)_nCR^9R^6$, $CHR^6(CH_2)_nO$, $CHR^6(CH_2)_nS$, $CHR^6(CH_2)_nOCO$, $CHR^6(CH_2)_nCO$, $COCHR^6(CH_2)_n$ or $SO_2CHR^6(CH_2)_n$; n represents an integer from 0 to 4; processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.

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MORPHOLIN-ACETAMIDE DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISEASES

This invention relates to novel chemical compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction. There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity, in which cytokine products, such as IL-4 and IL-5 released by Th2 T lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., **338**, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- (α) and CC- (β) chemokines, classified according to the spacing of two conserved cysteine residues near to the amino terminus of

the chemokine proteins. Chemokines bind to specific cell surface receptors belonging to the family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date, 9 members of CC chemokine receptors have been identified (CCR-1 to 9). Of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells (Luster, 1998). Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., **179**, 881-887 (1994), Lloyd et al., J. Exp. Med., **191**, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. *et al.*, (1997) J. Clin. Invest. **99** (2), 178-184), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., **188**, 157-167 (1998). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

A number of patent applications relating to CCR-3 antagonists have published before the filing date of this application. For example, EP 0 903 349, FR 2785902, WO 00/29377, WO 00/31032 and WO 00/31033 (all in the name of F.Hoffmann-La-Roche AG) disclose pyrrolidine, piperidine and piperazine based compounds which are all distinct from the compounds of the present invention.

WO 99/55324, WO 00/04003, WO 00/27800, WO 00/27835, WO 00/27843, WO 00/41685 and WO 00/53172 (all in the name of SmithKline Beecham Corporation) describe a variety of compounds as CCR-3 antagonists which are unrelated to the compounds of the present invention.

WO 00/34278 (Toray Industries Inc.) describe fused triazolo derived compounds as chemokine inhibitors.

WO 00/35449, WO 00/35451, WO 00/35452, WO 00/35453, WO 00/35454, WO 00/35876 and WO 00/35877 (Du Pont Pharmaceuticals Company) describe N-ureidoalkyl and heterocyclic piperidine compounds as CCR-3 antagonists.

WO 00/51607 and WO 00/51608 (Merck & Co. Inc.) describe a series of pyrrolidine modulators of chemokine receptor activity.

WO 00/53600 (Banyu Pharmaceutical Co. Ltd.) describes piperidine derivatives as inhibitors at the CCR-3 receptor.

WO 01/14333 (AstraZeneca UK Ltd.) describe substituted piperidine compounds as modulators of chemokine receptor activity.

EP 0 760 362 (Nisshin Flour Milling Co. Ltd.) describes morpholinoalkylurea derivatives which are disclosed as being useful in the treatment of digestive tract diseases.

JP 04208267A (Mitsui Seiyaku Kogyo KK) also describes morpholinoalkylurea derivatives which are disclosed as being useful as antiemetics, for activating peristalsis and ameliorating gastrointestinal function.

EP 243959A (Dainippon Pharm KK) describes O-substituted N-morpholinyl-alkyl-benzamide derivatives useful as gastrointestinal motility enhancing agents.

J0 1117-882-A (Dainippon Pharm KK) describes heterocyclic morpholinyl alkylenyl carboxamide derivatives useful as anti-emetics.

WO 00/71518 (Sepracor Inc) describes morpholinoalkylamide derivatives useful in the treatment of pain, drug addiction and tinnitus.

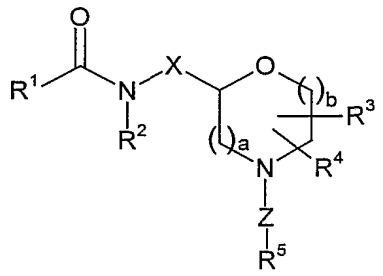
WO 97/48695 and WO 97/48397 (Klinge Pharma Gmbh) describe pyridyl alkane, alkene and/or alkyne acid amide compounds useful as cytostatic, immunomodulatory or immuno-suppressive agents.

Kato *et al.*, (1992) Chem. Pharm. Bull. **40(3)**, 652-660, Kato et al., (1991) J. Med. Chem. **34(2)**, 616-624 and Kato et al., (1990) J. Med. Chem. **33(5)**, 1406-1413 describe a series of morpholine benzamides which are disclosed as being selective and potent gastrokinetic agents.

We have now found a novel group of CCR-3 antagonist compounds which block migration/chemotaxis of eosinophils, consequently effecting anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil, basophil and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 (for review see Wells and Schwartz, Curr. Opin. Biotech., **8**, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). CCR-3 serves as a co-receptor for certain clinical strains of HIV-1 and facilitates viral entry (e.g Choe, H. *et al*, Cell, 1996, **85**, 1135-1148). A key ligand for CCR-3, eotaxin, blocked the process of HIV entry. Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

Thus, according to one aspect of the invention, we provide compounds of formula (I):



(I)

wherein:

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkynyl-Y^1-, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^2-Y^1-, -CN or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl;

X represents ethylene or a group of formula CR^eR^f wherein R^e and R^f independently represent hydrogen or C_{1-4} alkyl or R^e and R^f may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^3 and R^4 independently represent hydrogen or C_{1-4} alkyl;

Z represents a bond, CO, SO_2, $CR^9R^6(CH_2)_n$, $(CH_2)_nCR^9R^6$, $CHR^6(CH_2)_nO$, $CHR^6(CH_2)_nS$, $CHR^6(CH_2)_nOCO$, $CHR^6(CH_2)_nCO$, $COCHR^6(CH_2)_n$ or $SO_2CHR^6(CH_2)_n$;

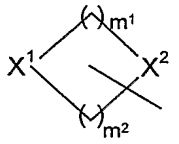
R^5 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl-C_{2-6} alkenyl- or a group of formula $-Y^2-J^1$;

R^6 represents hydrogen, C_{1-4} alkyl, $CONR^7R^8$ or $COOC_{1-6}$ alkyl;

a and b represent 1 or 2, such that a+b represents 2 or 3;

n represents an integer from 0 to 4;

J^1 and J^2 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{13} or sulphur, X^2 represents CH_2, oxygen, NR^{10} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{13}, NR^{10} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-COC_{3-8}$cycloalkyl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{11}R^{12}$, $-Y^3-CONR^{11}R^{12}$, hydroxy, oxo, $-Y^3-SO_2NR^{11}R^{12}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{14}C_{1-6}$ alkyl, $-Y^3-NR^{14}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{14}CONR^{11}R^{12}$, $-Y^3-NR^{14}COOR^{15}$ or $-Y^3-OCONR^{11}R^{12}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14} and R^{15} independently represent hydrogen or C_{1-6} alkyl;

R^{11} and R^{12} independently represent hydrogen or C_{1-6} alkyl or R^{11} and R^{12} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

M represents a C_{3-8} cycloalkyl or a C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

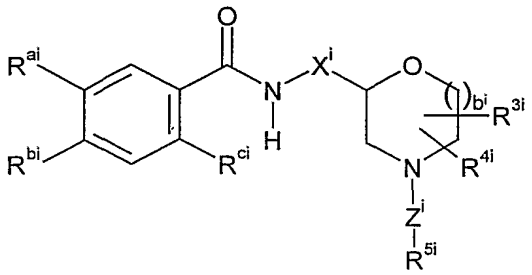
W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-6} alkyl, halogen or hydroxy groups;

t represents 0 or 1.

Y^1, Y^2 and Y^3 independently represent a bond or a group of formula $-(CH_2)_pCR^cR^d(CH_2)_q-$ wherein R^c and R^d independently represent hydrogen or C_{1-4} alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5;

and salts and solvates thereof.

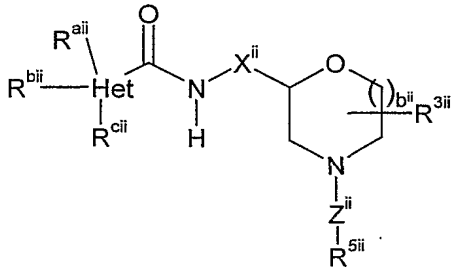
Specific groups of compounds of formula (I) which may be mentioned are those as defined above with the proviso that the compound of formula (I) is not a compound of formula $(I)^a$:



$(I)^a$

wherein R^{ai} represents hydrogen, halogen, nitro, SO_2NH_2, or mono- or di-(C_{1-4} alkylsulphamoyl; R^{bi} represents hydrogen, halogen, amino, nitro, $-N(CH_3)_2$ or C_{2-5} alkanoylamino (provided that at least one of R^{ai} and R^{bi} is not hydrogen); R^{ci} represents halogen, hydroxy, C_{1-6} alkoxy, cyano, C_{3-6} cycloalkyl, $-SCH_3$, amino or C_{2-5} alkoxycarbonyl; X^i represents methylene or ethylene; b^i represents 1 or 2; R^{3i} and R^{4i} represent hydrogen or C_{1-4} alkyl; and wherein the moiety $-Z^i$-R^{5i} represents heteroarylC_{1-3} alkyl (wherein heteroaryl represents furyl, thienyl, pyridyl or 1,2-benzisoxazolyl), phenyl-C_{3-5} alkenyl, naphthyl, $-C_{1-5}$ alkylenenaphthyl, $-C_{1-5}$ alkyleneOnaphthyl, $-C_{1-5}$ alkyleneCOnaphthyl, phenyl, $-C_{1-5}$ alkylenephenyl, $-C_{1-5}$ alkyleneOphenyl or $-C_{1-5}$ alkyleneCOphenyl (wherein phenyl is substituted by one to five members each independently selected from the group consisting of a halogen, C_{1-4} alkyl, trifluoromethyl, C_{1-4} alkoxy, nitro, cyano or amino) (compounds of formula $(I)^a$ are described in EP0243959A1); and/or

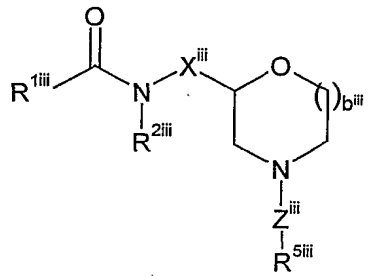
the proviso that the compound of formula (I) is not a compound of formula $(I)^b$:



$(I)^b$

wherein Het represents a heteroaryl moiety; R^{aii}, R^{bii} and R^{cii} represent hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, amino or NMe_2; X^{ii} represents methylene or ethylene; R^{3ii} represents hydrogen or C_{1-4} alkyl; b^{ii} represents 1 or 2; and wherein the moiety $-Z^{ii}$-R^{5ii} represents optionally substituted aryl-C_{1-5} alkyl- (compounds of formula $(I)^b$ are described in J01117-882A); and/or

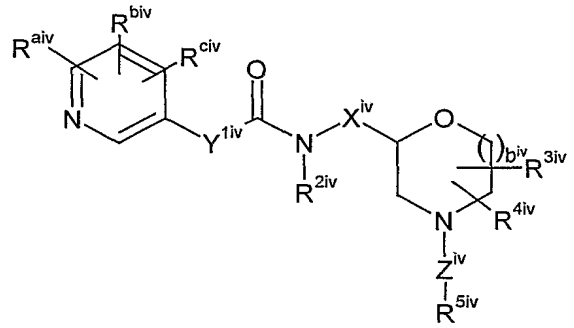
the proviso that the compound of formula (I) is not a compound of formula $(I)^c$:



$(I)^c$

wherein R^{1iii} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, heteroaryl or aryl; R^{2iii} represents C_{1-6} alkyl; X^{iii} represents ethylene or a group of formula $CR^{eiii}R^{fiii}$ wherein R^{eiii} and R^{fiii} independently represent hydrogen or C_{1-4} alkyl; R^{3iii} represents hydrogen or C_{1-4} alkyl; b^{iii} represents 1 or 2; Z^{iii} represents $CR^{9iii}R^{6iii}(CH_2)_{niii}$ (wherein R^{6iii} represents hydrogen or C_{1-4} alkyl and R^{9iii} represents hydrogen or C_{1-6} alkyl and niii represents 0 to 3); and R^{5iii} represents C_{1-6} alkyl, aryl, heteroaryl or C_{2-6} alkenyl (compounds of formula $(I)^c$ are described in WO00/71518A2); and/or

the proviso that the compound of formula (I) is not a compound of formula $(I)^d$:

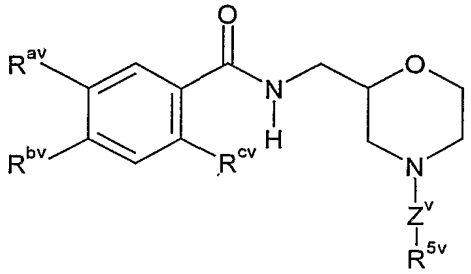


$(I)^d$

wherein R^{aiv} represents hydrogen, halogen, -CN, $-CF_3$, -OH, $-CONH_2$, -COOH, C_{1-6} alkyl, $-C_{2-6}$ alkenyl, $-C_{1-6}$ alkoxy, $-SCH_3$, C_{3-8} cycloalkyl, $-COOC_{1-6}$ alkyl, $-NHCOC_{1-6}$ alkyl, $-CON(C_{1-6}$ alkyl$)_2$, $-N(CH_3)_2$; R^{biv} represents hydrogen, halogen, -CN, OH, $-CF_3$, C_{1-6} alkyl or C_{1-6} alkoxy; R^{civ} represents hydrogen, halogen, C_{1-6} alkyl, $-CF_3$; Y^{1iv} represents C_{1-6} alkylene; R^{2iv} represents hydrogen or C_{1-6} alkyl; X^{iv} represents methylene or ethylene; R^{3iv} represents hydrogen or C_{1-4} alkyl; R^{4iv} represents hydrogen or C_{1-4} alkyl; b^{iv} represents 2; Z^{iv} represents $CR^{9iv}R^{6iv}(CH_2)_{niv}$, $CHR^{6iv}(CH_2)_{niv}CO$ (wherein R^{6iv} represents hydrogen or C_{1-4} alkyl and R^{9iv} represents hydrogen or methyl and niv represents 0 to 3) or $SO_2CHR^{6iv}(CH_2)_{niv}$ (wherein R^{6iv} represents hydrogen and niv represents 0); and R^{5iv} represents C_{1-6} alkyl, C_{3-6} alkenyl, phenyl, J^1 or heteroaryl (wherein said phenyl or heteroaryl may be optionally substituted by 1-3 halogen, CN, C_{1-6} alkyl, $-CF_3$, C_{3-8} cycloalkyl, hydroxy, C_{1-6} alkoxy, $-SCH_3$, COOH,

$COOC_{1-6}$ alkyl, nitro, amino or $-N(CH_3)_2$) (compounds of formula $(I)^d$ are described in WO97/48695A1 and WO97/48397A1); and/or

the proviso that the compound of formula (I) is not a compound of formula $(I)^e$:



$(I)^e$

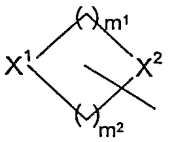
wherein R^{av} represents chlorine; R^{bv} represents amino; R^{cv} represents methoxy or ethoxy; and the moiety $-Z^v$-R^{5v} represents phenyl or C_{1-6} alkyl (such compounds of formula $(I)^e$ are described in Kato *et al.*, (1992) Chem. Pharm. Bull. 40(3), 652-660);

also wherein R^{av} represents chlorine; R^{bv} represents amino; R^{cv} represents methoxy or ethoxy; and the moiety $-Z^v$-R^{5v} represents $-CH_2$-phenyl wherein phenyl is substituted by 2-, 3- or 4-chlorine, 2-, 3- or 4-fluorine, 3- or 4-CF_3, 3- or 4-methoxy, 4-methyl, 4-nitro, 4-amino, 4-carboxymethyl, 3- or 4-cyano, 3,4-dichloro, 2,4-difluoro, 3,4-difluoro, 3,5-difluoro, 2,4,6-trimethyl (such compounds of formula $(I)^e$ are described in Kato et al., (1991) J. Med. Chem. 34(2), 616-624);

also wherein R^{av} represents hydrogen, bromine, chlorine, nitro or SO_2NH_2; R^{bv} represents amino, $-NMe_2$, $-NEt_2$ or $-NHCOCH_3$; R^{cv} represents methoxy, ethoxy, hydroxy or chlorine; and the moiety $-Z^v$-R^{5v} represents $-CH_2$-phenyl (such compounds of formula $(I)^e$ are described in Kato et al., (1990) J. Med. Chem. 33(5), 1406-1413).

A preferred set of compounds of formula (I) include compounds wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkynyl-Y^1-, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups; and

J^1 represents a moiety of formula (K):



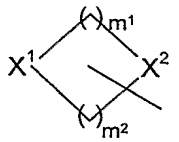
(K)

wherein X^1 represents oxygen, NR^{13} or sulphur, X^2 represents CH_2, oxygen, NR^{10} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{13}, NR^{10} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{11}R^{12}$, -Y^3-$CONR^{11}R^{12}$, hydroxy, oxo, -Y^3-$SO_2NR^{11}R^{12}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{14}C_{1-6}$ alkyl, -Y^3-$NR^{14}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{14}CONR^{11}R^{12}$, -Y^3-$NR^{14}COOR^{15}$ or -Y^3-$OCONR^{11}R^{12}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

A preferred subset of compounds of formula (I) include compounds wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

Z represents a bond, CO, $CR^9R^6(CH_2)_n$, $CHR^6(CH_2)_nO$, $CHR^6(CH_2)_nS$, $CHR^6(CH_2)_nOCO$, $CHR^6(CH_2)_nCO$; and

J^1 represents a moiety of formula (K):



(K)

wherein X^1 represents oxygen, nitrogen, NR^{13} or sulphur, X^2 represents CH_2, oxygen, nitrogen, NR^{10} or sulphur, m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when X^2 represents oxygen, nitrogen, NR^{10} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{11}R^{12}$, -Y^3-$CONR^{11}R^{12}$, hydroxy, oxo, -Y^3-$SO_2NR^{11}R^{12}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{14}C_{1-6}$ alkyl, -Y^3-$NR^{14}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{14}CONR^{11}R^{12}$, -Y^3-$NR^{14}COOR^{15}$ or -Y^3-$OCONR^{11}R^{12}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) and references to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-3 hetero atoms selected from nitrogen, oxygen and sulphur. References to 'heteroaryl' may also be extended to include references to mono- and bicyclic heterocyclic aromatic rings containing 4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. pyridinyl, pyrimidinyl, thiophenyl, furanyl, pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl. Further examples of monocyclic heterocyclic aromatic rings include pyrazinyl or tetrazolyl. Examples of bicyclic heterocyclic aromatic rings include eg. benzimidazolyl, quinolinyl or indolyl. Further examples of bicyclic heterocyclic aromatic rings include eg. benzotriazolyl, pyrrolopyridine, benzothiazolyl and quinoxalinyl. Carbocyclic and heterocyclic aromatic rings may be optionally substituted, e.g. by one or more C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, cyano, hydroxy, nitro, amino, W, $-N(CH_3)_2$, $-NHCOC_{1-6}$ alkyl, $-OCF_3$, $-CF_3$, $-COOC_{1-6}$ alkyl, $-OCHF_2$, $-SCF_3$, $-SO_2N(CH_3)_2$, $-SO_2CH_3$, $-SCH_3$, $-CONR^{16}R^{17}$ or $-SO_2NR^{16}R^{17}$ groups (wherein R^{16} and R^{17} independently represent hydrogen or C_{1-6} alkyl; R^{16} and R^{17} may also independently represent C_{3-8} cycloalkyl). Further substituents of carbocyclic and heterocyclic aromatic rings include –COOH and $-NHSO_2CH_3$. Yet further substituents include $-N(C_{1-6}alkyl)SO_2C_{1-6}alkyl$, $-N(SO_2C_{1-6}alkyl)_2$, $-NHCOCH_2N(C_{1-6}alkyl)_2$, $-NHCONHC_{1-6}alkyl$, $-CONH(CH_2)_2OC_{1-6}alkyl$, $-CONH(CH_2)_2N(C_{1-6}alkyl)_2$, $CON(C_{1-6}alkyl)_2$, C_{3-8}cycloalkyl, morpholinyl, –COmethylpiperazinyl and COmorpholinyl.

Examples of group J^1 include indolinyl, which may be optionally substituted.

Examples of group J^2 include thiomorpholinyl and piperidinyl, which may be optionally substituted, for example by t-butoxycarbonyl.

Examples of group M include tetrahydronaphthalenyl.

Examples of group W include piperidinyl, pyrrolidinyl, morpholinyl and piperazinyl which may be optionally substituted.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkylene and alkoxy shall be interpreted similarly.

References to C_{3-8} cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl.

Preferably, R^1 represents C_{1-6} alkyl (particularly butyl and $-(CH_2)_2CH(CH_3)_2$), C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-

(particularly wherein aryl represents phenyl and heteroaryl represents tetrazolyl, oxadiazolyl, thiazolyl or oxazolyl), heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1- (particularly wherein heteroaryl represents oxazolyl, thiazolyl, thiophenyl, pyrazolyl, pyrazinyl, furanyl, pyridinyl or tetrazolyl), C_{2-6} alkenyl-Y^1-, aryl-O-Y^1- (particularly wherein aryl represents phenyl), heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1- (particularly wherein C_{1-6} alkyl represents methyl), M-Y^1-, -CN, J^2-Y^1- or C_{3-8} cycloalkyl-Y^1- (particularly cyclopropyl and cyclohexyl) or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups.

Particularly, R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups.

More preferably, R^1 represents aryl-Y^1-, aryl-O-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1- or heteroaryl-$(O)_t$-heteroaryl-Y^1-, especially aryl-Y^1-, heteroaryl-Y^1, heteroaryl-$(O)_t$-heteroaryl-Y^1- or aryl-$(O)_t$-heteroaryl-Y^1-. In this definition, aryl preferably represents phenyl optionally substituted by one or more -SO_2-$N(CH_3)_2$, -SO_2CH_3, halogen (especially fluorine or chlorine), C_{1-6} alkyl (especially methyl), CH_3CONH-, -CF_3, CH_3O-, -$CONH_2$, $(CH_3)_2N$- or -SCH_3 groups. Further preferred phenyl substituents include -$NHSO_2CH_3$, -COOH, -$COOCH_3$ and -CONH-cyclopropyl. Yet further preferred phenyl substituents include –SO_2NHcyclopropyl, -$SO_2NHCH_2CH_3$, -SO_2NHCH_3, -$N(CH_3)SO_2CH_3$, -$N(SO_2CH_3)_2$, -$NHCOCH_2N(CH_3)_2$, -$NHCOCH(CH_3)_2$, -NH_2, -SO_2NH_2, -$NHCONHCH_3$, -NO_2, -$CONH(CH_2)_2OCH_3$, -$CONHCH(CH_3)_2$, -$CONH(CH_2)_2OH$, -$CONH(CH_2)_2N(CH_3)_2$, -$CON(CH_3)_2$, -$CONHCH_2CH_3$, -$CONHCH_3$, -$COCH_3$, -$COCH(CH_3)_2$, -CN, -OH, –CO-4-methyl-1-piperazinyl and -COmorpholinyl. Heteroaryl preferably represents indolyl, thiophenyl, oxazolyl, pyrazolyl, thiazolyl, pyrimidinyl or furanyl optionally substituted with one or more C_{1-6} alkyl (especially methyl), CH_3O- or halogen (especially bromine) groups. Heteroaryl also preferably represents tetrazolyl or pyrazinyl. Further preferred groups which heteroaryl may represent include benzotriazolyl, pyrrolopyridine, benzothiazolyl, pyridinyl, quinoxalinyl and imidazolyl. Suitable heteroaryl substituents include halogen (especially bromine), -$COCH_3$, -$COOCH_3$, -CH_3, -$CH(CH_3)_2$, morpholinyl, cyclopropyl, -$CH_2CH(CH_3)_2$ and -$CH=C(CH_3)_2$.

A most particularly preferred group of compounds are those in which R^1 is aryl-$(O)_t$-heteroaryl-Y^1- especially wherein heteroaryl represents optionally substituted oxazolyl, (especially oxazolyl substituted by methyl), aryl represents phenyl and t represents 0.

Especially preferred R^1 is aryl-Y^1-, particularly when aryl represents phenyl optionally substituted by any of the above substituents, most especially phenyl substituted by $-SO_2NH_2$.

Preferably, Y^1 represents a bond, C_{1-6} alkylene, C_{3-8} cycloalkyl or $-CHCH_3$, particularly C_{1-6} alkylene or C_{3-8} cycloalkyl, most preferably methylene, ethylene or cyclopropyl, especially methylene or cyclopropyl, most especially methylene.

Preferably, R^2 represents hydrogen.

Preferably, X represents methylene.

Preferably, R^3 and R^4 independently represent hydrogen or methyl, especially hydrogen.

Preferably, Z represents a bond, CO, $CR^9R^6(CH_2)_n$, $CHR^6(CH_2)_nO$, $CHR^6(CH_2)_nS$, $CHR^6(CH_2)_nOCO$ or $CHR^6(CH_2)_nCO$.

More preferably, Z represents a bond, CO, $CHR^6(CH_2)_n$, $CHR^6(CH_2)_nO$ (particularly $(CH_2)_2O$) or $CHR^6(CH_2)_nCO$, more particularly $CHR^6(CH_2)_n$ or $CHR^6(CH_2)_nCO$, most preferably CH_2, $(CH_2)_3$, $CHCH_3$ or CH_2CO, especially CH_2 or CH_2CO, most especially CH_2.

Preferably, R^5 represents C_{2-6} alkenyl (particularly $-CH_2CH(CH_3)=CH_2$), aryl, heteroaryl or a group of formula $-Y^2$-J^1, more preferably aryl, heteroaryl or a group of formula $-Y^2$-J^1, most preferably monocyclic aryl, heteroaryl or a group of formula $-Y^2$-J^1, especially aryl or $-Y^2$-J^1, particularly phenyl which may be optionally substituted. We also especially prefer R^5 to represent heteroaryl, particularly thiophenyl which may be optionally substituted. Other groups which heteroaryl preferably represents include benzoxadiazolyl, benzothiadiazolyl or benzothiophenyl which may be optionally substituted. We most particularly prefer R^5 to represent phenyl optionally substituted by one or more (eg. 1, 2 or 3) halogen groups. Other preferred substituents for phenyl include -CN and $-CF_3$. We also most particularly prefer R^5 to represent thiophenyl optionally substituted by one or more (eg. 1, 2 or 3) halogen groups.

Especially preferred R^5 groups are dichlorophenyl, difluorophenyl, fluorophenyl, chlorothiophenyl, chlorophenyl and trifluorophenyl, most especially dichlorophenyl, difluorophenyl, fluorophenyl and chlorothiophenyl.

Most preferred R^5 is dichlorophenyl (particularly 3,4-dichlorophenyl, 2,3-dichlorophenyl and 2,5-dichlorophenyl), 4-fluorophenyl and 3,4-difluorophenyl.

Most especially preferred R^5 is dichlorophenyl, particularly 3,4-dichlorophenyl.

Preferably, Y^2 represents a bond.

Preferably, J^1 represents indolinyl, particularly indolin-1-yl.

Preferably, J^2 represents optionally substituted piperidinyl (particularly piperidinyl substituted by $-COOC_{1-6}$alkyl eg. $-COOC(CH_3)_3$) or thiomorpholinyl (particularly dioxidothiomorpholinyl) or dioxidothiomorpholinyl.

Preferably, Y^3 represents a bond.

Preferably, R^6 represents hydrogen.

Preferably, R^7 and R^8 represent hydrogen.

Preferably, R^9 represents hydrogen.

Preferably, R^{10} and R^{13} independently represent hydrogen or methyl, especially hydrogen.

Preferably, R^{11} and R^{12} independently represent hydrogen or methyl or R^{11} and R^{12} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring, especially hydrogen or methyl.

Preferably, R^{14} and R^{15} independently represent hydrogen or methyl.

Preferably, R^{16} and R^{17} independently represent hydrogen, methyl, ethyl, isopropyl, 2-hydroxyethyl, 2-methoxyethyl, cyclopropyl or 2-(dimethylamino)ethyl. Most preferably, R^{16} and R^{17} independently represent hydrogen or cyclopropyl.

Preferably, R^c and R^d independently represents hydrogen or methyl, most preferably hydrogen or R^c and R^d together with the carbon atom to which they are attached preferably forms cyclopropyl.

Preferably, R^e and R^f both represent hydrogen.

Preferably, a and b both represent 1.

Preferably, n represents 0, 1 or 2, more preferably 0.

Preferably, p and q independently represent 0 or 1 such that p+q represent 0-1. Most preferably, p and q both represent 0.

Preferably, t represents 0.

Preferably, W represents pyrrolidinyl or piperidinyl, especially pyrrolidinyl.

Preferably, X^1 represents sulphur, oxygen or NR^{11}. More preferably, X^1 represents oxygen or NR^{11}.

Preferably, X^2 represents CH_2, oxygen or NR^{12}.

Preferably, m^1 and m^2 independently represent an integer from 1 to 2, such that $m^1 + m^2$ is in the range from 3 to 4.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If

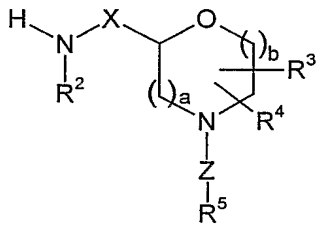
appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates. Examples of solvates include hydrates.

When compounds of formula (I) contain chiral centres, the invention extends to mixtures of enantiomers (including racemic mixtures) and diastereoisomers as well as to individual enantiomers. Generally it is preferred to use a compound of formula (I) in the form of a single enantiomer.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) which comprises:

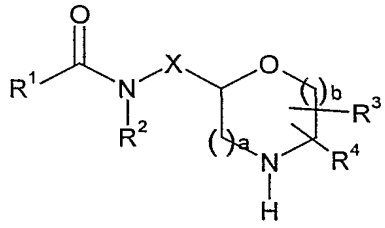
(a) acylation of a compound of formula (II)



(II)

or a protected derivative thereof wherein R^2, R^3, R^4, R^5, X, Z, a and b are as described above, with a compound of formula R^1COOH or an activated derivative thereof, wherein R^1 is as described above; or

(b) reacting a compound of formula (III)



(III)

or a protected derivative thereof wherein R^1, R^2, R^3, R^4, X, a and b are as defined above, with a compound of formula

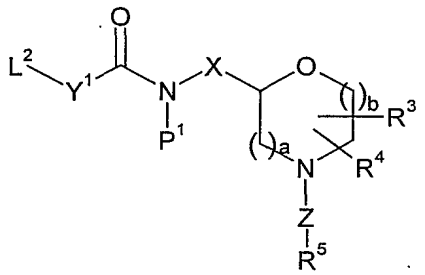
L^1-Z-R^5, wherein Z and R^5 are as defined above and L^1 represents a suitable leaving group; or

(c) deprotecting a compound of formula (I) which is protected; or

(d) interconversion of other compounds of formula (I).

We also provide a further process according to the invention for preparing a compound of formula (I) which comprises:

(e) forming a compound of formula (I) wherein R^1 represents heteroaryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1- or heteroaryl-$(O)_t$-heteroaryl-Y^1- (wherein said Y^1 group is attached to heteroaryl via a heterocyclic nitrogen atom) and R^2 represents hydrogen which comprises reacting a compound of formula (IV)



(IV)

or a protected derivative thereof wherein R^3, R^4, R^5, X, Y^1, Z, a and b are as defined above, L^2 represents a suitable leaving group, such as a halogen atom eg. bromine and P^1 represents a solid phase resin bound protecting group, such as one described for process (c), with a heterocyclic compound defined by the R^1 groups heteroaryl, aryl-$(O)_t$-heteroaryl or heteroaryl-$(O)_t$-heteroaryl above wherein said heteroaryl group contains at least one NH atom, followed by removal of the solid phase resin bound protecting group; or

(f) forming a compound of formula (I) wherein Z represents $CR^9R^6(CH_2)_n$ and R^9 represents hydrogen which comprises reacting a compound of formula (III) or a protected derivative thereof with a compound of formula $R^6CO(CH_2)_nR^5$, followed by reduction of the resultant imine; or

(g) forming a compound of formula (I) wherein Z represents CO by reacting a compound of formula (III) or a protected derivative thereof with a compound of formula R^5COOH or an activated derivative thereof.

Process (a) may be effected simply by the reaction of a compound of formula (II) with R^1COOH which may typically be achieved using an oven eg. a microwave oven at a power of 600W for 4 minutes. Examples of activated derivatives of R^1COOH which may be employed in this reaction include acid halides and anhydride derivatives (eg. the acid chloride). Alternatively, process (a) may be performed in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylammonium hexafluorophosphate (HATU) and a suitable base, eg. N,N-diisopropylethylamine in a suitable solvent, eg. N,N-dimethylformamide at a suitable temperature, eg. room temperature. Process (a) may also be performed in the presence of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide hydrochloride in the presence of a suitable base, eg. N,N-diisopropylethylamine and a suitable solvent, eg. dichloromethane or N,N-dimethylformamide, at a suitable temperature, eg. room temperature. Further, process (a) may be performed in the presence of 1,1'-carbonyldiimidazole in the presence of a suitable solvent, eg. N,N-dimethylformamide at a suitable temperature, eg. room temperature. Process (a) may also be performed in the presence of a suitable base such as polyvinylpyridine and a suitable solvent, such as dichloromethane at a suitable temperature such as room temperature.

Process (b) may be performed in the presence of a suitable solvent eg. N,N-dimethylformamide, optionally in the presence of N,N-diisopropylethylamine at a suitable temperature eg. room temperature. Examples of suitable leaving groups (L^1) include halogen, eg. chlorine.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis, or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker) or a 2,6-dimethoxy-4-[2-(polystyrylmethoxy)ethoxy]benzyl, which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic aromatic substitution, ester hydrolysis or amide bond formation. Alternative conditions for process (d) include t-butoxycarbonyl group addition or removal and sulphonylation.

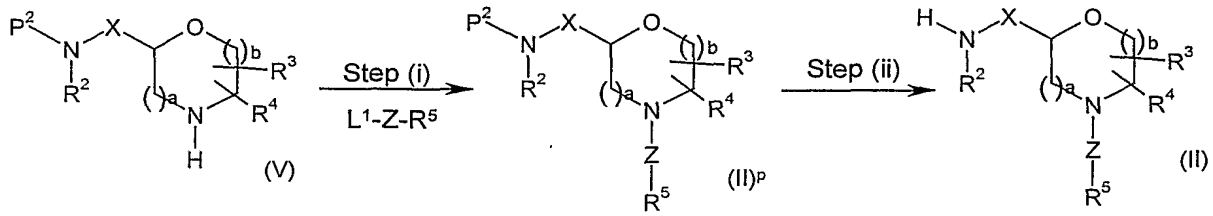
Process (e) may be performed using a suitable base, eg. potassium tert-butoxide and a suitable solvent, eg. N,N-dimethylformamide, at a suitable temperature, eg. 60°C.

Process (f) may be performed in the presence of a suitable acid eg. acetic acid and a suitable reducing agent, eg. sodium triacetoxyborohydride in a suitable solvent, eg. dichloromethane at a suitable temperature, eg. room temperature.

Process (g) may be performed in the presence of suitable reagents, eg. 1,-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride and 1-hydroxybenzotriazole in the

presence of a suitable base, eg. N,N-diisopropylethylamine and a suitable solvent eg. N,N-dimethylformamide at a suitable temperature, eg. room temperature.

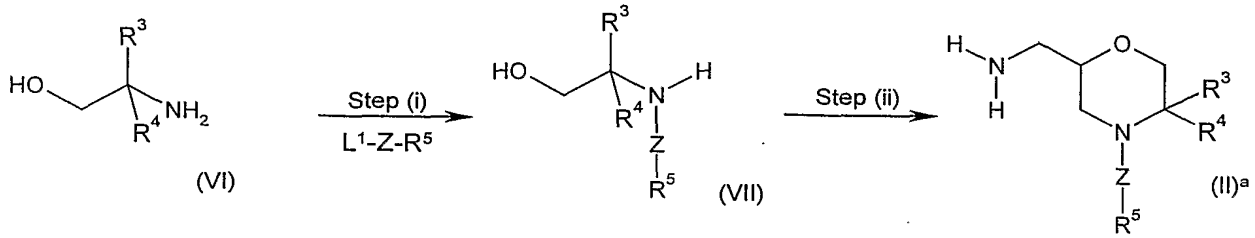
Compounds of formula (II) may be prepared according to the following process:



wherein R^2, R^3, R^4, R^5, X, a, b and Z are as defined above and L^1 represents a suitable leaving group eg. chlorine and P^2 represents a suitable protecting group eg. one mentioned above, such as $-COCF_3$. Step (i) comprises the use of a suitable solvent eg. N,N-dimethylformamide in the presence of suitable reagents eg. sodium iodide and potassium carbonate at a suitable temperature eg. room temperature. Alternatively step (i) may comprise the use of a suitable solvent eg. N,N-dimethylformamide, in the presence of a suitable base such as N,N-diisopropylethylamine at a suitable temperature eg. room temperature. Step (ii) comprises deprotection under conventional conditions appropriate for the protecting groups. When P^2 represents $-COCF_3$, deprotection may be achieved by the use of water and methanol in the presence of potassium carbonate at room temperature.

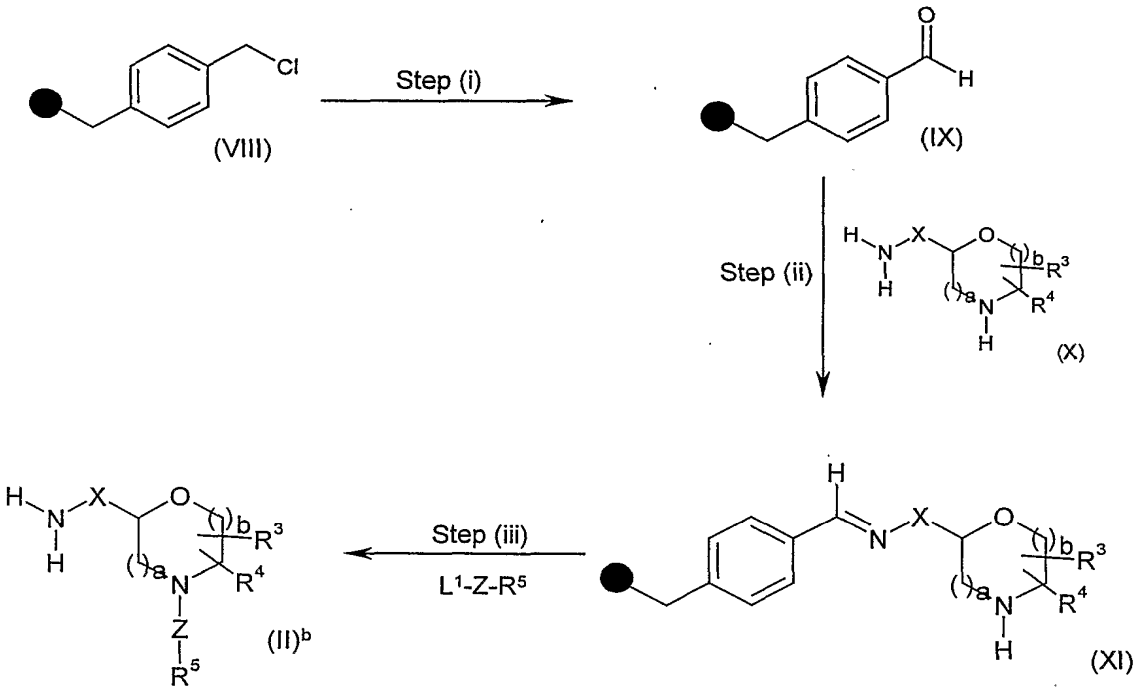
Compounds of formula $(II)^p$ may also be prepared by reductive amination of compounds of formula (V) in an analogous manner to that described in process (f) above.

Compounds of formula (II) wherein R^2 represents hydrogen, X represents methylene, a and b represent 1 and R^3 and R^4 are both attached to the morpholine ring at the 5-position may be prepared according to the following process:



wherein R^3, R^4 and R^5 and Z are as defined above and L^1 represents a suitable leaving group eg. chlorine. Step (i) comprises heating in the absence of solvent at between 50 and 60°C. Step (ii) comprises heating with 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione at 80°C under nitrogen, followed by stirring with concentrated sulphuric acid at 150°C.

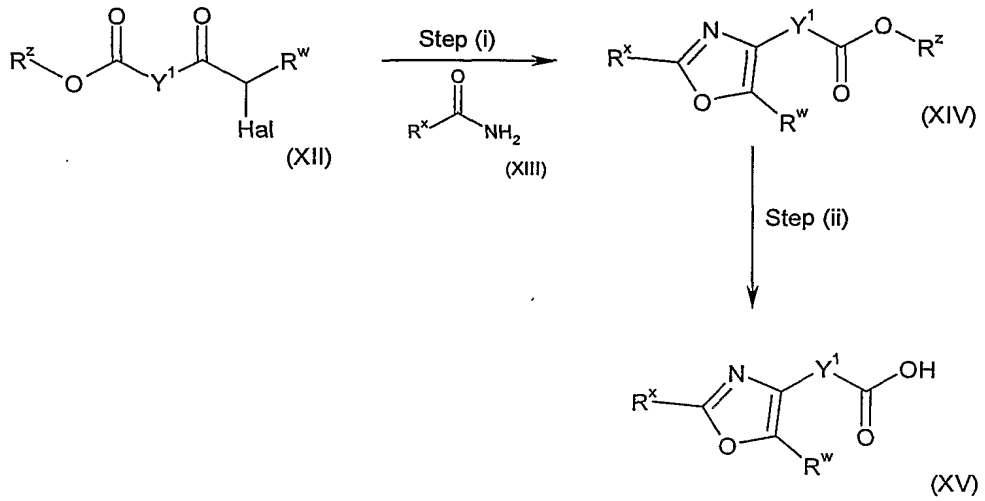
Compounds of formula (II) wherein R^2 represents H may be prepared according to the following process:



wherein R^3, R^4, R^5, X, a, b and Z are as defined above and L^1 represents a suitable leaving group eg. chlorine. Step (i) comprises heating a compound of formula (VIII; Merrifield Resin) with sodium carbonate in a suitable solvent eg. dimethylsulphoxide at a suitable temperature eg. 150°C. Step (ii) comprises reacting a compound of formula (IX) with a compound of formula (X) in the presence of a suitable solvent eg. tetrahydrofuran at a suitable temperature eg. room temperature. Step (iii) comprises the use of suitable solvent eg. N,N-dimethylformamide and a suitable base eg. N,N-diisopropylethylamine at a suitable temperature eg. 70°C, followed by deprotection under conventional conditions appropriate for the Merrifield resin protecting group eg. acid catalysed hydrolysis.

Compounds of formula R^1COOH used in process (a) above (and activated derivatives thereof) are either known compounds or may be synthesised by known methods.

For example, compounds of formula R^1COOH wherein R^1 represents heteroaryl-Y^1, aryl-$(O)_t$-heteroaryl-Y^1- or heteroaryl-$(O)_t$-heteroaryl-Y^1- (wherein the heteroaryl moiety linked to Y^1 represents 1,3-oxazol-4-yl and t represents 0) may be prepared according to the following process:



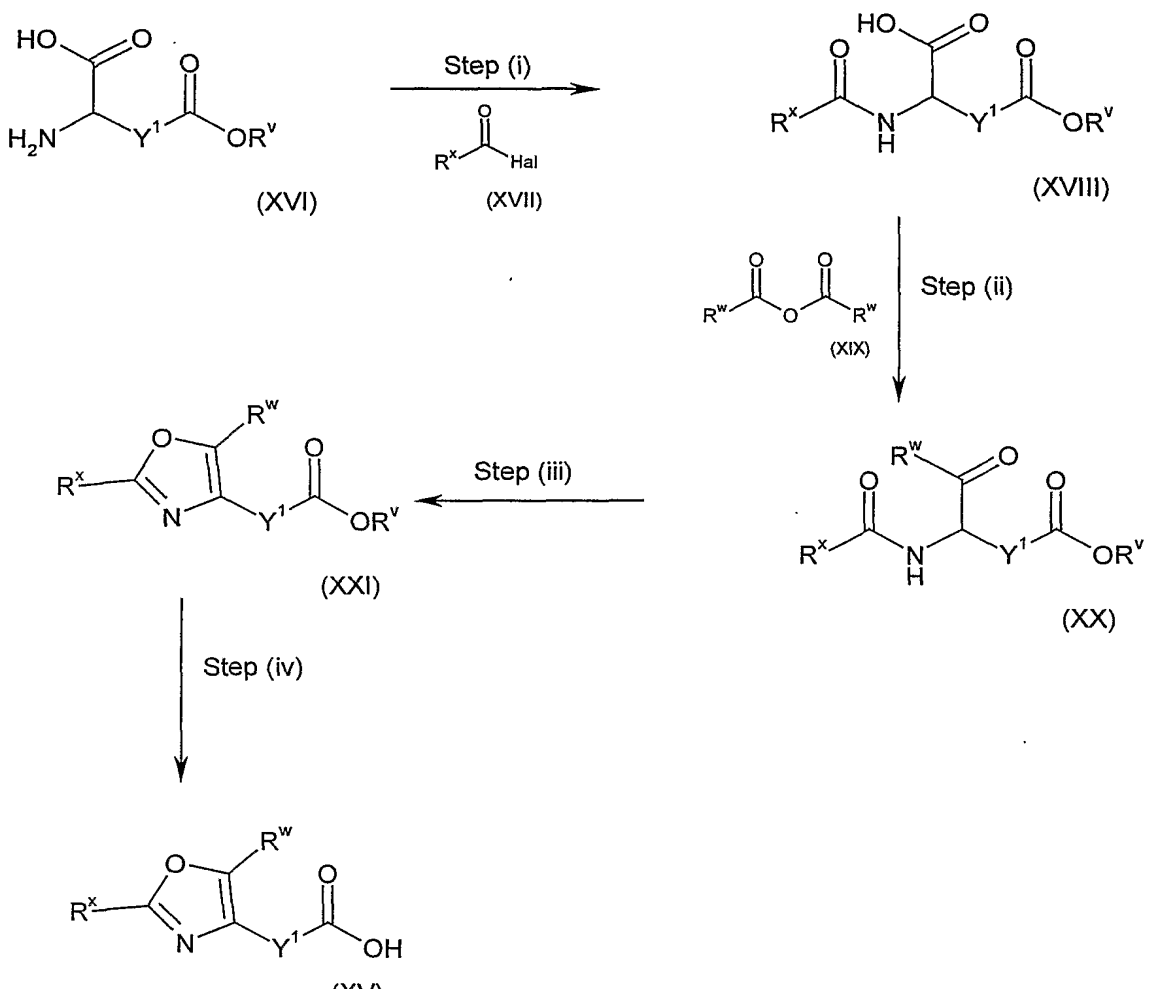
wherein R^w represents a suitable substituent described above for a heteroaryl group, especially C_{1-6} alkyl, R^x represents C_{1-6} alkyl, aryl or heteroaryl, R^z represents C_{1-6} alkyl, especially ethyl, Hal represents a halogen atom, especially bromine and Y^1 is as defined above.

Compounds of formula (XII) may be prepared by following the procedure described in Svendsen and Boll (1973) Tetrahedron 29, 4251-4258.

Step (i) may typically be performed in the presence of a suitable solvent, eg. toluene at a suitable temperature eg. at 140°C and using suitable conditions, eg. Dean-Stark conditions.

Step (ii) may typically be performed in the presence of a suitable alkali, eg. sodium hydroxide and suitable solvents, eg. water and ethanol at a suitable temperature, eg. 70°C.

Compounds of formula R^1COOH wherein R^1 represents heteroaryl-Y^1, aryl-$(O)_t$-heteroaryl-Y^1- or heteroaryl-$(O)_t$-heteroaryl-Y^1- (wherein the heteroaryl moiety linked to Y^1 represents 1,3-oxazol-4-yl and t represents 0) may also be prepared according to the following process:



wherein R^v represents C_{1-6} alkyl, especially methyl, R^w represents a suitable substituent described above for a heteroaryl group, especially C_{1-6} alkyl, R^x represents C_{1-6} alkyl, aryl or heteroaryl, Hal represents a halogen atom, especially chlorine and Y^1 is as defined above.

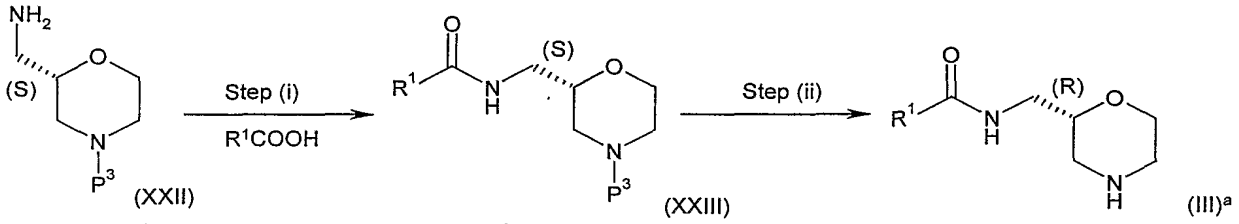
Step (i) may typically be performed in the presence of a suitable base, eg. pyridine, at a suitable temperature, eg. from 0°C to room temperature.

Step (ii) may typically be performed in the presence of a suitable base, eg. pyridine at a suitable temperature, eg. 90°C, followed by the addition of water at a suitable temperature, eg. 90°C.

Step (iii) may typically be performed in the presence of a suitable reagent, eg. phosphorus oxychloride and a suitable solvent, eg. toluene, under suitable conditions, eg. 110°C.

Step (iv) may typically be performed in the presence of a suitable alkali eg. 2M aqueous sodium hydroxide, and a suitable solvent, eg. ethanol at a suitable temperature, eg. room temperature.

Compounds of formula (III) as the R-isomer, wherein R^2 represents hydrogen, X represents methylene, a and b represent 1 and R^3 and R^4 both represent hydrogen may be prepared according to the following process:



wherein R^1 is as defined above and P^3 is a suitable protecting group, eg. benzyl.

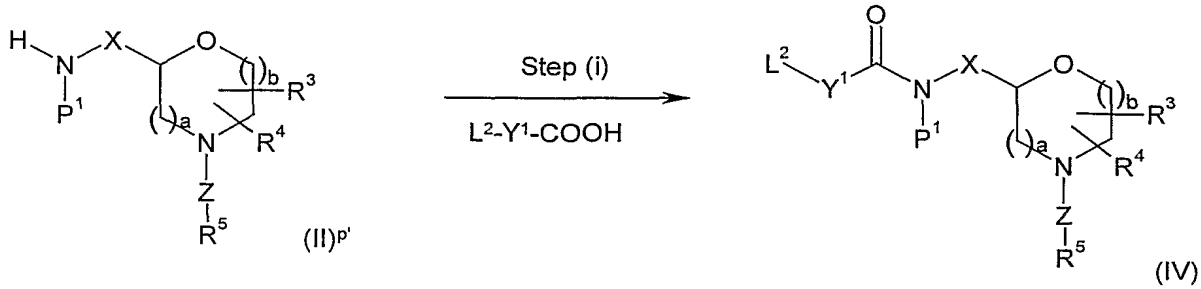
Compounds of formula (XXII) may be prepared as described in EP0995746.

Step (i) typically comprises the use of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in the presence of a suitable base, eg. N,N-diisopropylethylamine and a suitable solvent, eg. N,N-dimethylformamide, at a suitable temperature, eg. room temperature.

Step (ii) typically comprises a simple deprotection reaction, eg. which may comprise the use of 10% palladium on activated carbon in the presence of ammonium formate and a suitable solvent, eg. ethanol.

Compounds of formula (III) as the S-isomer, wherein R^1 is as defined above, may be prepared by an analogous process.

Compounds of formula (IV) may be prepared according to the following process:



wherein R^3, R^4, R^5, X, Y^1, Z, a and b are as defined above, L^2 represents a suitable leaving group, such as a halogen atom, eg. bromine and P^1 represents a solid phase resin bound protecting group, such as one described in process (c).

Step (i) typically comprises the use of a suitable reagent, eg. 1,3-diisopropylcarbodiimide in the presence of one or more suitable solvents, eg. dichloromethane and N,N-dimethylformamide.

Compounds of formula (V), (VI), (VIII), (X), (XII), (XIII), (XVI), (XVII), (XIX) and (XXII) are either known or may be prepared in accordance with known procedures.

Compounds of formula L^1-Z-R^5, $R^6CO(CH_2)_nR^5$, R^5COOH, L^2-Y^1-COOH and heterocyclic compounds defined by the R^1 groups heteroaryl, aryl-$(O)_t$-heteroaryl or heteroaryl-$(O)_t$-heteroaryl above are also either known or may be prepared in accordance with known procedures.

Compounds of formula (III) may be prepared in accordance with processes analogous to those described above for compounds of formula (I), employing suitable protection for the morpholine (or analogue) NH, e.g. t-butoxycarbonyl protection.

Compounds of formula (II), (III) and (IV) in their protected and deprotected form and salts and solvates thereof are also claimed as an aspect of the invention.

Compounds of the invention may be tested for in vitro and in vivo biological activity in accordance with the following assays.

(a) CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5μg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in binding buffer (HEPES 50 mM, $CaCl_2$ 1 mM, $MgCl_2$ 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [^{125}I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30μM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 μl. Competition binding data were analysed by fitting the data with a four parameter logistic equation. Data are presented as the mean pIC_{50} values (negative logarithm of the concentration of compound which inhibits [^{125}I]eotaxin binding by 50%) from at least two experiments.

(b) Eosinophil chemotaxis Assay.

Compounds were evaluated for their inhibitory effect on eosinophil chemotaxis. Eosinophils were purified from human peripheral blood by standard CD16 cell depletion using a Miltenyi cell separation column and a magnetic Super Macs magnet as previously described (Motegi & Kita, 1998; J.Immunology. 161:4340-6). Cells were re-suspended in RPMI 1640/10% FCS solution and incubated with calcein-AM (Molecular Probes) at 37°C for 30 mins. Following incubation, the eosinophils were centrifuged at 400g for 5 min and re-suspended in RPMI/FCS at 2.2 million/ml. Cells were then incubated in the presence of increasing concentration of compounds (1 pM to 30 μM) at 37°C for 30 mins. For control responses

cells were incubated with RPMI/FCS only. The agonist eotaxin (either a concentration response curve or for the functional inhibition curves an EC_{80} concentration) was added to the lower chamber of a 96 well chemotaxis plate (5 μm filter: Receptor Technologies). Eosinophils (50 μl of 2 million/ml cells) were added to the top chamber of the filter plate and incubated at 37°C for 45 mins. Cells remaining on top of the chemotaxis filter were removed and the number of eosinophils which had migrated were quantified by reading the plate on a fluorescent plate reader. Inhibition curves for the effect of compounds on eosinophil chemotaxis were analysed by fitting the data with a four parameter logistic equation. Functional pK_i values (fpK_i) were generated using the equation below (Lazareno & Birdsall, 1995. Br.J.Pharmacol 109: 1110-9).

$$fpKi = \frac{IC_{50}}{1+\left[\frac{[Agonist]}{EC_{50}}\right]}$$

(c) Guinea-pig Ovalbumin Model

Inhibition of Eosinophil Infiltration and Hyper-Reactivity in the Guinea Pig

In a method based on that described by Danahay *et al.*, 1997, ovalbumin sensitised guinea pigs were dosed with mepyramine (30mg kg^{-1} ip) to protect against anaphylactic bronchospasm. Test compounds, dissolved in 10% DMSO and 90% PEG200, were given by the oral route, 30 minutes before ovalbumin challenge (10 minutes breathing of an aerosol generated from a 0.5% solution of ovalbumin). Hyper-reactivity of the airways to the thromboxane mimetic U46619, was measured 24 hours after ovalbumin challenge in un-restrained animals using a whole body plethysmograph (Buxco Ltd., USA). The guinea pigs were then sacrificed and the lungs lavaged. Total and differential leukocyte counts were then obtained for the bronchoalveolar lavage fluid and the percentage reduction in eosinophil accumulation determined (Sanjar *et al.*, 1992). Data was presented as the inhibitory effect of the specified dose expressed as a percentage of the vehicle control response.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD) and rhinitis. Another disease of the respiratory tract in which the compounds of the invention have potentially beneficial effects is sinusitis. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's

disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure. Furthermore, compounds of the invention may be used to treat nephritis, skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions and diseases of the central nervous system which have an inflammatory component eg. Alzheimer's disease, meningitis, multiple sclerosis and AIDS dementia. Compounds of the present invention may also be of use in the treatment ofnasal polyposis, conjunctivitis or pruritis. Additionally, the compounds of the present invention may be of use in the treatment of viral diseases such as HIV.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome. Other diseases for which the compounds of the present invention may be beneficial are other hypereosinophilic diseases such as Churg-strauss syndrome. Additionally, eosinophilia is commonly found in parasitic diseases, especially helminth infections, and thus the compounds of the present invention may be useful in treating inflammation arising from hyper-eosinophilic states of diseases such as hydatid cyst (Echinococcus sp.), tapeworm infections (Taenia sp.), blood flukes (schistosomiasis), and nematode (round worms) infections such as:- Hookworm (Ancylostoma sp.), Ascaris, Strongyloides, Trichinella, and particularly lymphatic filariasis including Onchocerca, Brugia, Wucheria (Elephantiasis).

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis. Preferred diseases of principle interest include asthma and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis. Further diseases also of principle interest include inflammatory diseases of the gastrointestinal tract such as inflammatory bowel disease.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as pharmaceuticals, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as pharmaceuticals, particularly in the treatment of patients with inflammatory conditions, eg. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition eg. asthma or rhinitis, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying

agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof), anti-histamines (eg methapyrilene or loratadine) or antiinfective agents (eg. antibiotics, antivirals).

It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more

preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

The compounds of the invention have the advantage that they may be more efficacious, show greater selectivity, have fewer side effects, have a longer duration of action, be more bioavailable when administered by the oral route, have more ready and economic synthesis, or have other more desirable properties than similar known compounds.

The invention may be illustrated by reference to the following examples:

Examples

General Experimental Details

Standard Automated Preparative HPLC column, conditions and eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco+ 5μm (100mm x 22mm internal diameter) column eluted with a mixture of solvents consisting of i) 0.1% trifluoroacetic acid in water and ii) 0.1% trifluoroacetic acid in acetonitrile, the eluent being expressed as the percentage of ii) in the solvent mixture, at a flow rate of 4ml per minute.

Mass Directed Automated Preparative HPLC column, conditions and eluent

Mass directed automated preparative high performance liquid chromatography was carried out using an LCABZ+ 5μm (5cm x 10mm internal diameter) column, employing gradient elution using two solvent systems, (A) 0.1% formic acid in water, and (B) 95% acetonitrile and 0.5% formic acid in water, at a flow rate of 8ml min^{-1}. Mass spectrometry was carried out using a VG Platform Mass Spectrometer, with an HP1100 Diode Array Detector and Accurate Flow Splitter.

Normal Phase Automated Preparative HPLC Column - conditions

Normal phase automated preparative high performance liquid chromatography (normal phase autoprep HPLC) was carried out using a Nucleosil silica 5μm (100mm x 20mm internal diameter) column eluted with an ethyl acetate:heptane two-step gradient (i) 0% to 25% ethyl acetate over 7min followed by (ii) 25% to 100% ethyl acetate over 5.5min; at a flow rate of 30ml/min.

LC/MS System

Three alternative Liquid Chromatography Mass Spectroscopy (LC/MS) Systems were used:

System A

This system used a 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents:A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3 ml per minute. The following gradient protocol was used: 100% A for 0.7mins; A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100%B for 1.1mins; return to 100% A over 0.2mins.

System B

This system used a 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents:A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1 ml per minute. The following gradient protocol was used: 100% A for 1.0min; A+B mixtures, gradient profile 0 – 100% B over 9.0mins; hold at 100%B for 3.0mins; return to 100% A over 2.0mins.

System C

This system used a 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents:A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1 ml per minute. The following gradient protocol was used: 100% A for 2.0mins; A+B mixtures, gradient profile 0 – 100% B over 20mins; hold at 100%B for 5.0mins; return to 100% A over 2.0mins; hold at 100% A for 1.0mins.

All LC/MS systems (apart from the Mass Directed Automated Preparative HPLC system) used a micromass spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 a.m.u.

Thermospray Mass Spectra

Thermospray Mass Spectra were determined on a HP 5989A engine mass spectrometer, +ve thermospray, source temperature 250°C, probe temperatures 120°C (stem), 190°C (tip), detection mass range 100-850 a.m.u. Compounds were injected in 10μl of a mixture of solvents comprising 65% methanol and 35% 0.05M aqueous ammonium acetate, at a flow rate of 0.7ml/min.

Normal phase analytical HPLC method

Normal phase automated analytical high performance liquid chromatography (normal phase analytical HPLC) was carried out using a Nucleosil silica 3μm (150mm x 4.6mm internal diameter) column eluted with an ethyl acetate:heptane two-step gradient (i) 0% to 40% ethyl acetate over 7 min followed by (ii) 40% to 100% ethyl acetate over 2.5 min; at a flow rate of 2ml/min.

Standard chiral analytical HPLC system

This system used a 250 x4.6mm Chiralpak AD 10µm column, eluting with absolute ethanol:heptane mixtures at a flow rate of 1ml per minute, with UV detection at 215nm.

Standard chiral preparative HPLC system

This system used a Chiralpak AD column (2cm x 25cm), eluting with absolute ethanol:heptane mixtures (15ml/min over 25mins, UV detection at 215nm).

Solid phase extraction (ion exchange)

'SCX' refers to Isolute Flash SCX-2 sulphonic acid solid phase extraction cartridges.

Organic/aqueous phase separation with hydrophobic frits

'Hydrophobic frit' refers to a Whatman polypropylene filter tube fitted with a PTFE frit, pore size 5.0µm.

All temperatures are in °C.

Intermediates

Intermediate 1: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (Chem Abs No. 40172-06-3, 0.980g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (1.10g) was heated at 80°C under nitrogen for 3h. The resulting solid mass was treated with concentrated sulphuric acid (1.5ml) then stirred at 150°C for 24h. The mixture was treated with water (100ml) then washed with ethyl acetate (2x100ml). The dark aqueous phase was basified to ~pH 12 using 5M aqueous sodium hydroxide, then extracted with ethyl acetate (2x100ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (1.02g).

LC-MS (System A): Rt 1.6min.

Intermediate 1 (Alternative procedure): [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine

To a stirred solution of Intermediate 42 (2.97g) in methanol (15ml) and water (5ml) was added potassium carbonate (5.53g). The mixture was stirred at 22°C for 18h before the methanol was removed in vacuo. Water (25ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). The combined organic phases were washed with water (5ml) and saturated aqueous sodium chloride solution (10ml) before drying over sodium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 75:8:1 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated in vacuo to give the title compound as a colourless oil (1.85g).

LC/MS (System A) R_t 1.77 min, Mass Spectrum *m/z* 275 [MH^+].

Intermediate 1A: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine salt with para-toluenesulphonic acid 1:1

A solution of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.25g) and 2-chloroacrylonitrile (1.0ml) in tetrahydrofuran (3ml) was heated at 40°C for 66h. The solvent was evaporated in vacuo to leave a gum. The residue was redissolved in tetrahydrofuran (20ml) and cooled to 0-5°C. Potassium tert-butoxide (1.2g) was added portionwise to this solution over 10min and the mixture was stirred at 0-5°C for a further 45min. The mixture was diluted with water (20ml) and ethyl acetate (20ml), the phases were separated and the organic phase was washed with 20% w/w aqueous sodium chloride solution. The organic phase was dried over sodium sulfate and the solvent was evaporated in vacuo to leave a gum (2.75g).

A portion of this gum (0.22g) in tetrahydrofuran (1ml) was treated dropwise with a 1M solution of borane.tetrahydrofuran complex in tetrahydrofuran (2.44ml) at 15-25°C. The mixture was stirred at 15-25°C for 16h, and methanol (3ml) was added dropwise. The mixture was stirred for a further 5h and the solvent was evaporated in vacuo. The residue was redissolved in ethyl acetate (4ml) and p-toluenesulfonic acid monohydrate (0.123g) was added. The mixture was heated at 50°C for 20min, and the suspension was cooled to 15-25°C and stirred for 15min. The mixture was filtered, washed with ethyl acetate and dried to give the title compound (0.123g) as a white solid.

LC/MS (System A) R_t 1.75 min. Mass spectrum *m/z* 275/277 [MH^+]

Intermediate 2: 2-[(3,4-Dichlorobenzyl)amino]-2-methylpropan-1-ol

3,4-Dichlorobenzyl chloride (3.95g) was added to 2-amino-2-methylpropan-1-ol (17.8g) and the mixture was stirred at 60°C under nitrogen for 2h. Excess amine was removed by distillation under vacuum and the residue was partitioned between saturated aqueous sodium bicarbonate (100ml) and ethyl acetate (100ml). The phases were separated, the organic layer was washed with water (4x100ml) and brine (100ml), dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a white solid (4.7g).

LC-MS (System A): Rt 2.07min.

Intermediate 3: 1-[4-(3,4-Dichlorobenzyl)-5,5-dimethylmorpholin-2-yl]methanamine

A mixture of Intermediate 2 (0.260g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (0.205g) was heated at 80°C under nitrogen for 3h. The mixture was treated with concentrated sulphuric acid (0.3ml) then stirred at 150°C for 18h. The mixture was treated with water (25ml) then washed with ethyl acetate (2x25ml). The dark aqueous phase was basified to ~pH 11 using 5M aqueous sodium hydroxide then extracted with ethyl acetate

(2x25ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (0.225g).

LC-MS (System A): Rt 1.92min.

Intermediate 4: 2-[(3,4-Dichlorobenzyl)amino]propan-1-ol

3,4-Dichlorobenzyl chloride (0.988g) was added to 2-amino-1-propanol (4.10g) and the mixture was stirred at 50°C under nitrogen for 2h. The mixture was partitioned between saturated aqueous sodium bicarbonate (100ml) and ethyl acetate (100ml) and the phases were separated. The organic layer was washed with water (4x100ml) and brine, dried (Na_2SO_4) then concentrated under vacuum to give the title compound as a white solid (0.935g).

LC-MS (System A): Rt 2.13min.

Intermediate 5: 1-[(*cis*)-4-(3,4-Dichlorobenzyl)-5-methylmorpholin-2-yl]methanamine (2:1 mixture with *trans* isomer)

A mixture of Intermediate 4 (0.470g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (0.410g) was heated at 80°C under nitrogen for 5h. The mixture was treated with concentrated sulphuric acid (0.6ml) then stirred at 150°C for 42h. The mixture was treated with water (50ml) then washed with ethyl acetate (2x50ml). The dark aqueous phase was basified to ~pH 11 using 5M aqueous sodium hydroxide then extracted with ethyl acetate (2x50ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (0.42g).

LC-MS (System A): Rt 1.74min.

Intermediate 6: 2-{[3-(3,4-Dichlorophenyl)propyl]amino}ethanol

4-(3-Bromopropyl)-1,2-dichlorobenzene (Chem Abs No. 29648-26-8, 1.30g) was added to ethanolamine (2.8ml) and the mixture stirred at 60°C under nitrogen for 2h. The mixture was concentrated under vacuum at 80°C and the residue was partitioned between saturated aqueous sodium bicarbonate (100ml) and ethyl acetate (100ml). The phases were separated, the aqueous layer was re-extracted with ethyl acetate (100ml) and the combined organic extracts were washed with water (2x100ml) and brine then dried (Na_2SO_4). The solution was concentrated under vacuum to give the title compound as a pale yellow liquid (1.10g).

LC-MS (System A): Rt 2.40min.

Intermediate 7: 1-{4-[3-(3,4-Dichlorophenyl)propyl]morpholin-2-yl}methanamine

A mixture of Intermediate 6 (1.05g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (1.10g) were heated at 80°C under nitrogen for 2h. The mixture was treated with

concentrated sulphuric acid (1.5ml) then stirred at 150°C for 18h. The mixture was treated with water (100ml) then washed with ethyl acetate (2x100ml). The dark aqueous phase was basified to ~pH 11 using 5M aqueous sodium hydroxide then extracted with ethyl acetate (2x100ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (0.980g). LC-MS (System A): Rt 2.05min.

Intermediate 8: 1-[4-(2,3-Dichlorobenzyl)morpholin-2-yl]methanamine hydrochloride

A mixture of chloromethylpolystyrene-divinylbenzene (Merrifield resin, loaded at 4.0 mmol g^{-1}) (5.0g) and sodium hydrogen carbonate (14.5g) in dimethylsulphoxide (80ml) was heated at 150° C for 8h. The solution was allowed to cool, left to stand for 24h, then filtered. The solid was washed successively with water (3 x 100ml), tetrahydrofuran (3 x 100ml) and diethyl ether (3 x 100ml), then dried in vacuo to give the formylpolystyrene as a yellow solid which was not characterised. A portion of this solid (1.0g) was washed with tetrahydrofuran (5x10ml) and transferred to a round bottomed flask. 1-Morpholin-2-ylmethanamine dihydrochloride (0.435g) was dissolved in methanol (10ml) and loaded equally onto two solid phase extraction columns (Isolute SCX sulphonic acid, 10g each) which had been prepared by application of methanol. Elution with methanol, then .880 ammonia:methanol 10:90 gave a clear colourless oil (0.280g). This was added in tetrahydrofuran (2.3ml) to the round bottomed flask containing formylpolystyrene and the mixture stirred for 24h at 20°C. The mixture was then filtered, and the solid washed with tetrahydrofuran:methanol 1:1 to leave N-{[4-(polystyrene resin)phenyl]methylidene}-1-morpholin-2-ylmethanamine as a yellow solid which was not characterised. Two portions of this solid (2x50mg) in two thick walled glass vials (Reactivials) were each treated with N,N-dimethylformamide (1.25ml), N,N-diisopropylethylamine (0.097ml) and 1,2-dichloro-3-(chloromethyl)benzene (0.076ml), and the mixture was stirred at 70°C for 20h, then allowed to cool. The mixtures were combined, filtered and washed sequentially with N,N-dimethylformamide (10x10ml) and tetrahydrofuran (5x10ml), then treated with tetrahydrofuran:2M aqueous hydrochloric acid solution 3:1 (3ml). After 2h shaking at 20°C, the mixture was filtered, washed with tetrahydrofuran (4x5ml) and the filtrate and washings concentrated in vacuo to give the title compoundas white crystals (0.060g).

1HNMR (MeOD) 7.85 (1H,dd,aromatic CH), 7.78 (1H,dd,aromatic CH), 7.53 (1H,t,aromatic CH), 4.72 (2H,AB,CH_2), 4.30 – 4.23 (2H,m,2xCH), 4.05 (1H,br.t,CH), 3.65 (1H,br.d,CH), 3.58 (1H,br.d,CH), 3.47 (1H,dd,CH), 3.30 – 3.22 (2H,m,2xCH), 3.08 (1H,br.m,CH).

Intermediate 9: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine

Intermediate 1 (racemic mixture, 8g) was separated into its single enantiomers by preparative chiral-HPLC. The separation was carried out using a 2" x 22cm Chiralpak AD 20µm column, Merck self pack DAC system, eluting with 95:5:0.1 (v/v) heptane : absolute ethanol: diethylamine (flow rate: 55ml/min over 40min, UV detection 225nm); sample load preparation: 400mg sample in 20ml 3:2 (v/v) absolute ethanol: system eluent.

The title compound (2.49g) was obtained with preparative HPLC retention time 23.0 min.

Intermediate 9A: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1

35% Hydrazine in water (1.8ml) was added to a slurry of Intermediate 41 (5g) in industrial methylated spirits (75ml), and the mixture was heated to reflux. Chloroform (75ml) was added and the mixture was heated under reflux for 65h. The reaction mixture was cooled to 0-4°C and allowed to stand for 15min. The by-product phthalhydrazide was removed by vacuum filtration and washed with chloroform (50ml). The filtrate was washed with water (50ml, 25ml), dried ($MgSO_4$), and the solvent evaporated in vacuo to give an oil. This was dissolved in methanol (20ml), which was evaporated in vacuo to give an oil. The oil was dissolved in methanol (100ml) and D-tartaric acid (1.05g) was added. The mixture was heated to and maintained at reflux for 30min. The solution was cooled to 45-50°C, then seeded. The slurry was held at this temperature for 30min, then cooled to 0-4°C and allowed to stand for 30min. The product was isolated by filtration to give the title compound as a white solid (2.59g).

A sample of the crude D-tartrate salt (500mg) was dissolved in water (1.4ml). Methanol (23ml) was added to give a slurry which was heated to reflux to give a solution. The mixture was stirred at reflux for 30min, then cooled slowly, seeding at 55°C. The resultant slurry was cooled to 0-4°C and allowed to stand 30min. The product was isolated by filtration to give the title compound as a white solid (0.355g).

ee: 91.6%ee

LC/MS (System A) R_t 1.75 min. Mass spectrum *m/z* 275/277 [MH^+]

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Intermediate 9A (Alternative Procedure): 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1

Intermediate 1 (0.613g) was dissolved in methanol (12.3ml). D-Tartaric acid (0.335g) was added and the slurry was heated to reflux for 50min. The mixture was allowed to cool to 0-5°C and the precipitate isolated by filtration to give the title compound as a white solid (0.4g).
ee: 76%ee

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Intermediate 10: 1-[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine

Intermediate 10 was prepared in an analogous manner to Intermediate 9 yielding the title compound (2.24g) with preparative HPLC retention time 27.8 min.

Intermediate 10A: 1-[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with L-tartaric acid 1:1

[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine (Intermediate 1) (0.500g) was dissolved in methanol (5ml). L-Tartaric acid (0.273g) was added and the mixture was heated to ~65°C to give a milky slurry, and maintained at this temperature for 1h. Further methanol (5ml) was added and the mixture left to cool slowly to 15-25°C, then cooled further to 0-4°C. The mixture was stirred for 30min at this temperature and the product isolated by filtration to give the title compound as a white solid (0.38g).
ee: 78%

LC/MS (System A) R_t 1.75 min. Mass spectrum *m/z* 275/277 [MH^+]

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 10.5min.

Intermediate 11: Ethyl [2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetate

A suspension of 4-fluorobenzamide (12.9g) and ethyl 4-bromo-3-oxopentanoate (Chem Abs No. 36187-69-6; 5.24g) in anhydrous toluene (120ml) was heated at 140°C for 19 h, using a Dean-Stark trap. The solution was allowed to cool, filtered, and the residual solid washed with toluene (30ml). The combined filtrate and washings were concentrated in vacuo to give a brown oil, which was purified by Biotage flash chromatography on silica gel (90g column), eluting with ethyl acetate:cyclohexane (5:95, 7.5:92.5, 10:90), to give thetitle compound as a yellow solid (2.98g).

LC/MS (System A) Rt 3.26 min. Mass spectrum *m/z* 264 [MH^+].

Intermediate 12: [2-(4-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetic acid

Intermediate 11 (2.98g) in ethanol (25ml) was treated with aqueous sodium hydroxide (2.5M, 18ml) and the solution stirred at 70°C for 3.5h then allowed to cool. The material was concentrated in vacuo to remove the ethanol, then the aqueous phase was washed with

ethyl acetate (30ml). The aqueous phase was adjusted to pH1 by addition of aqueous hydrochloric acid (5M) and the desired acid was extracted into ethyl acetate (1 x 100ml, 1 x 50ml). The combined organic phases were washed with dilute aqueous sodium chloride, dried (Na_2SO_4), filtered and the solution concentrated in vacuo to give the title compound as a cream solid (2.54g).

LC/MS (System A) Rt 2.85 min. Mass Spectrum *m/z* 236 [MH^+].

Intermediate 13: 1-{4-[(5-Chlorothien-2-yl)methyl]morpholin-2-yl}methanamine

Intermediate 13 was prepared in an analogous manner to Intermediate 1 (Alternative procedure) from Intermediate 19 and 2-chloro-5-(chloromethyl)thiophene, followed by a deprotection reaction yielding the title compound.

Intermediate 14: 1-{(2S)-4-[(5-Chlorothien-2-yl)methyl]morpholin-2-yl}methanamine

Intermediate 13 was separated into its single enantiomers by chiral preparative HPLC to give the title compound in an analogous manner to the separation of Intermediate 1 to yield Intermediate 9.

LCMS (system A) R_t 25.2min.

Chiral Preparative HPLC retention time 25.2min

Intermediate 14A: 1-{(2R)-4-[(5-Chlorothien-2-yl)methyl]morpholin-2-yl}methanamine

Intermediate 14A was prepared in an analogous manner to Intermediate 14 yielding the title compound.

LCMS (system A) R_t 34min.

Chiral Preparative HPLC retention time 34min.

Intermediate 15: N-{[(2S)-4-Benzylmorpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

A mixture of (5-methyl-2-phenyl-oxazol-4-yl)-acetic acid (0.263g), 1-hydroxylbenzotriazole (0.163g), and N,N-diisopropylethylamine (0.211ml) in N,N-dimethylformamide (3ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.232g). The mixture was stirred for 5min, treated with 1-[(2S)-4-benzylmorpholin-2-yl]methanamine (prepared in accordance with EP 0 995 746 A1; 0.192g), and the solution was stirred at 22°C for 18h. The mixture was partitioned between dichloromethane (20ml) and saturated aqueous sodium hydrogen carbonate (10ml). The phases were separated in a hydrophobic frit; the organic phase was loaded onto a solid phase extraction cartridge (10g SCX) and eluted with methanol, followed by .880 ammonia:methanol 10:90 to give the title compound as a colourless gum (0.394g).

LC/MS (System A) R_t 2.42 min. Mass spectrum *m/z* 406 [MH^+].

Chiral analytical HPLC, eluent 10% EtOH/n-heptane, R_t 18.55 min.

Intermediate 15A: N-{[(2R)-4-Benzylmorpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

Prepared in an analogous manner to Intermediate 15 from 1-[(2R)-4-benzylmorpholin-2-yl]methanamine (prepared in accordance with EP 0 995 746 A1) to obtain the R isomer.

Chiral analytical HPLC eluent 10% EtOH/n-heptane, R_t 16.296 min.

Intermediate 16: 2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)-N-[(2R)-morpholin-2-ylmethyl]acetamide

A mixture of Intermediate 15 (0.192g) and ammonium formate (0.4g) in absolute ethanol (2ml) was treated with 10% palladium on activated carbon (0.1g). After 1.5h the mixture was treated with ammonium formate (0.6g) and stirred under nitrogen for a further 15.5h.

The mixture was filtered through celite and the residue washed with absolute ethanol (20ml). The solvent was removed at reduced pressure to leave a gum. The residue was partitioned between ethyl acetate (20ml) and 2N sodium hydroxide (20ml). The phases were separated and the aqueous phase extracted with ethyl acetate (10ml). The combined organic extracts were filtered through Whatman silicone treated filter paper and the solvent removed at reduced pressure to give the title compound (0.077g) as a colourless gum.

LC/MS (System A) R_t 2.14 min. Mass spectrum *m/z* 316 [MH^+].

Intermediate 17: 2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)-N-[(2S)-morpholin-2-ylmethyl]acetamide

Intermediate 17 was prepared in an analogous manner to Intermediate 16 from Intermediate 15A yielding the title compound.

Intermediate 18: {3-[(Methylsulfonyl)amino]phenyl}acetic acid

Methanesulphonylchloride (1.70ml) was added to a stirred mixture of 3-aminophenylacetic acid (3.2g) and sodium carbonate (5.44g) in water (36ml), and the mixture was heated at 85°C with stirring for 4h, allowed to cool and acidified with conc. hydrochloric acid to pH2. After leaving to stand at approximately 4°C for 18h, a solid was filtered off, and the residue washed with water and ether. The aqueous and ether filtrates were combined and evaporated in vacuo to give a solid, which was dissolved in hot water; the solution was filtered whilst still hot and the filtrate left to cool before standing at 4°C for 18h. The precipitated solid was filtered, washed with a small quantity of cold water and dried in vacuo to give the title compound as a pale yellow solid (0.417g).

^{1}H nmr (400MHz, d_6 DMSO) 12.35 (1H, br, s, COOH), 9.74 (1H s, NH), 7.27 (1H, dd, CH), 7.13-7.08 (2H, m, 2xCH), 6.99 (1H, br, d, CH), 3.54 (2H, s, CH_2), 2.98 (3H, s CH_3)

LCMS (system A) R_t 2.07min. Mass Spectrum *m/z* =247 [MNH_4^+] *m/z* =228 [MH^+].

Intermediate 19: 2,2,2-Trifluoro-N-(morpholin-2-ylmethyl)acetamide

To a stirred solution of morpholin-2-ylmethylamine (3.1g) in methanol (70ml) under nitrogen was added an ethereal solution of ethyl-α,α,α-trifluoroacetate (5ml in 20ml ether) which had been washed with saturated aqueous sodium bicarbonate, water and brine, and dried. The mixture was stirred for 30 min at 22°C before removal of all volatiles in vacuo. The residue was dissolved in methanol (10ml) and the volatiles again removed in vacuo to give the title compound as a white crunchy foam (4.9g).

Thermospray Mass Spectrum *m/z* 213 [MH^+].

Intermediate 20: 1-[4-(3,4-Difluorobenzyl)morpholin-2-yl]methanamine

Intermediate 20 was prepared in an analogous manner to Intermediate 1 (Alternative Procedure) from Intermediate 19 and 3,4-difluorobenzyl bromide, followed by deprotection to yield the title compound.

Intermediate 21: 1-[4-(4-Fluorobenzyl)morpholin-2-yl]methanamine

Intermediate 21 was prepared in an analogous manner to Intermediate 1 (Alternative Procedure) from Intermediate 19 and 4-fluorobenzyl chloride, followed by deprotection to yield the title compound.

Intermediate 22: 1-[(2S)-4-(4-Fluorobenzyl)morpholin-2-yl]methanamine

Intermediate 21 was separated into its single enantiomers by chiral preparative HPLC to give the title compound in an analogous manner to the separation of Intermediate 1to yield Intermediate 9.

LCMS (system A) R_t 18.43min.

Chiral Preparative HPLC Retention time 18.43min.

Intermediate 23: 1-[(2R)-4-(4-Fluorobenzyl)morpholin-2-yl]methanamine

Intermediate 23 was prepared in an analogous manner to Intermediate 22yielding the title compound.

LCMS (system A) R_t 26.56min.

Chiral Preparative HPLC Retention time 26.56min.

Intermediate 24: [(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methylamine

Intermediate 24 was prepared in an analogous manner to Intermediate 9

Preparative chiral HPLC retention time 26.1min

Intermediate 25: [(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methylamine

Intermediate 25 was prepared in an analogous manner to Intermediate 9

Preparative chiral HPLC retention time 25.3min

Intermediate 26: [(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methylamine

Intermediate 26 was prepared in an analogous manner to Intermediate 9

Preparative chiral HPLC retention time 28.3

Intermediate 27: 1-[(*cis*)-4-(2,5-dichlorobenzyl)-5-methylmorpholin-2-yl]methanamine (2:1 mixture with *trans* isomer)

Intermediate 27 was made in an analogous manner to Intermediate 5

LC-MS (System A): Rt 1.88mins Mass Spectrum *m/z* 289 [MH^+]

Intermediate 28: 2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]-N-[(2R)-morpholin-2-ylmethyl]acetamide

Intermediate 28 was prepared in an analogous manner to Intermediate 16

LC-MS (System A): Rt 2.21mins Mass Spectrum *m/z* 334 [MH^+]

Intermediate 29: [4-(3-Fluorobenzyl)morpholin-2-yl]methylamine

A mixture of Intermediate 19 (0.300g) and N,N-diisopropylethylamine (0.372ml) in N,N-dimethylformamide (5ml) was treated with 3-fluorobenzyl bromide (0.295g). The solution was stirred at 20°C under nitrogen for 24h. The mixture was partitioned between dichloromethane (10ml) and saturated aqueous potassium carbonate (10ml). The phases were separated and the organic phase applied to an ion exchange cartridge (10g Isolute SCX, prewashed with methanol). The SCX cartridge was eluted with methanol (40ml) followed by 10% 0.880 ammonia in methanol (40ml) and the appropriate fractions were concentrated in vacuo. The residue was dissolved in methanol (2ml) and treated with aqueous 2N sodium hydroxide (2ml). The solution was stirred at 20°C for 24h. The mixture was partitioned between dichloromethane (15ml) and water (20ml). The aqueous extract was washed with dichloromethane (15ml) and the combined organic extracts concentrated to give the title compound as a colourless gum (0.150g).

Thermospray Mass spectrum *m/z* 225 [MH^+].

Intermediate 30: tert-Butyl [(2S)-4-(3,4-dichlorobenzoyl)morpholin-2-yl]methylcarbamate

A mixture of 3,4-dichlorobenzoic acid (0.5g), 1-hydroxybenzotriazole (0.376g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.432g), and N,N-diisopropylethylamine (0.485ml) in N,N-dimethylformamide (10ml) was stirred at 20°C for 10min. The mixture was treated with tert-butyl (2R)-morpholin-2-ylmethylcarbamate (0.500g, known compound WO 9639407A1) and stirred at 20°C for 24h. The mixture was partitioned between ethyl acetate (75ml) and 2N aqueous hydrochloric acid (50ml). The phases were separated and the organic extract washed with 2N aqueous hydrochloric acid (50ml),

saturated aqueous sodium hydrogen carbonate (2x50ml), dried ($MgSO_4$) and filtered. The solvent was removed in vacuo to give the title compound as a yellow oil, (0.774g).

LCMS (system A) R_t 3.24min Mass Spectrum *m/z* 389 [MH^+].

Intermediate 31: 1-[(2S)-4-(3,4-dichlorobenzoyl)morpholin-2-yl]methanamine hydrochloride

Intermediate 30 (0.770g) was treated with 4.0M hydrogen chloride in dioxane (8ml). The mixture was stirred at 20°C for 30min. The solvent was removed in vacuo to give the title compound as a white solid (0.592g).

LCMS (system A) R_t 2.04min Mass Spectrum *m/z* 289 [MH^+]

Intermediate 32: Methyl 4-oxo-3-[(pyridin-3-ylcarbonyl)amino]pentanoate

Nicotinyl chloride hydrochloride (178mg) was added to a stirred suspension of aspartic acid β-methyl ester hydrochloride (183mg) in pyridine at 0°C with stirring under nitrogen, and the mixture was stirred at 0°C for 1.5h and at room temperature for 0.5h. Acetic anhydride (0.37ml) was added, and the mixture was heated at 90°C for 2h. Water (0.6ml) was added and heating continued for 15min before the mixture was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was evaporated in vacuo to give a yellow oil (110mg).

LC-MS (System A) Rt 1.86min. Mass Spectrum *m/z* 251 [MH^+].

Intermediate 33: Methyl (5-methyl-2-pyridin-3-yl-1,3-oxazol-4-yl)acetate

Intermediate 32 (110mg) was treated with phosphorous oxychloride (0.51ml) in toluene (2ml) and the mixture heated under reflux for 3.5h. The mixture was poured into ice cold saturated aqueous sodium bicarbonate (30ml) and extracted with dichloromethane (20ml). The organic layer was evaporated in vacuo to give a yellow gum (111mg).

LC-MS (System A) Rt 2.30min. Mass Spectrum *m/z* 233 [MH^+].

Intermediate 34: (5-Methyl-2-pyridin-3-yl-1,3-oxazol-4-yl)acetic acid

Intermediate 33 (111mg) was dissolved in tetrahydrofuran (2ml) and water (0.2ml) and lithium hydroxide (12mg) added. The mixture was stirred at 22°C for 17h and heated at 60°C for 2h. Ethanol (3ml) and 2N aqueous sodium hydroxide (1ml) were added, and stirring was continued at 22°C for 2h. The mixture was applied to a sulphonic acid ion exchange cartridge (10g Isolute SCX) and eluted with methanol followed by 10% triethylamine in methanol. Evaporation of the triethylamine containing fraction gave the title compound as a gum (46mg).

LC-MS (System A) Rt 2.12min. Mass Spectrum *m/z* 219 [MH^+].

Intermediate 35: Ethyl 4-(methylthio)butanoate

A solution of ethyl 4-bromobutyrate (0.26g) in N,N-dimethylformamide (3ml) was treated with sodium thiomethoxide (0.103g), and the mixture stirred at room temperature overnight. The mixture was partitioned between water (10ml) and dichloromethane (10ml), and the organic layer was washed with 1:1 saturated aqueous sodium chloride and water (10ml). The organic layers were evaporated in vacuo to give the title compound as a clear oil (0.135g).

NMR ($CDCl_3$) 4.06δ(2H, q, CH_2), 2.46δ(2H, t, CH_2), 2.35δ(2H, t, CH_2), 2.03δ(3H, s, CH_3), 1.85δ(2H, m, CH_2), 1.18δ(3H, t, CH_3).

Intermediate 36: Ethyl 4-(methylsulfonyl)butanoate

A solution of Intermediate 35 (0.126g) in dry dichloromethane (5ml) was treated with m-chloroperoxybenzoic acid (0.27g) portion-wise over ~5min. The mixture was stirred at room temperature overnight, treated with saturated aqueous sodium carbonate solution (10ml) and stirred for ~5min. The organic layers were separated using a hydrophobic frit and evaporated in vacuo to give the title compound as a pale yellow oil (0.133g).

NMR ($CDCl_3$) 4.15δ(2H, q, CH_2), 3.11δ(2H, t, CH_2), 2.93δ(3H, s, CH_3), 2.52δ(2H, t, CH_2), 2.17δ(2H, m, CH_2), 1.28δ(3H, t, CH_3).

Intermediate 37: 4-(Methylsulfonyl)butanoic acid

To a solution of Intermediate 36 (0.130g) in ethanol (2ml), was added 2N aqueous sodium hydroxide (0.75ml). The mixture was stirred at room temperature under nitrogen overnight. The solution was evaporated in vacuo to remove the ethanol, and applied to a solid phase extraction cartridge (Isolute SCX sulphonic acid column, 2g). The cartridge was eluted with methanol (15ml) and the solvent concentrated in vacuo to give the title compound as a clear oil (0.110g).

NMR (MeOD) 3.09δ(2H, m, CH_2), 2.88δ(3H, s, CH_3), 2.41δ(2H, t, CH_2), 1.98δ(2H, m, CH_2).

Intermediate 38: Methyl [5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]acetate

A mixture of 4-fluorobenzamidoxime (1.54g) and dimethyl malonate (5.7ml) was heated under reflux in *para*-xylene (20ml) for 2h. The mixture was cooled, washed with 1M aqueous hydrochloric acid, the organic phase separated and dried ($MgSO_4$) and the solvent evaporated in vacuo. The colourless oily residue was diluted with toluene and the toluene evaporated three times; the residue was re-dissolved in dichloromethane and the solvent evaporated under a stream of nitrogen to give the title compound as colourless crystals (1.59g).

Thermospray Mass Spectrum *m/z* 237 [MH^+], 254 [MNH_4^+]

Intermediate 39: Methyl [3-(aminosulfonyl)phenyl]acetate

0.880 Ammonia (0.027ml) was added to a stirred solution of methyl [3-(chlorosulfonyl)phenyl]acetate (0.35g) in a 1:1 mixture of dichloromethane and acetonitrile (1.75ml), and the mixture was stirred at 22°C for 2h. The mixture was allowed to stand for a further 18h, and the solvent was evaporated in vacuo. The residue was re-dissolved in dichloromethane and applied to a silica gel cartridge (10g Varian Bond Elut, pre-conditioned with dichloromethane). The cartridge was eluted with dichloromethane, chloroform, ether, ethyl acetate, acetone, acetonitrile and methanol (1 column volume each), the fractions containing the product evaporated in vacuo, and the residue passed down a 5g silica gel cartridge which was prepared and eluted in an identical manner. The product containing fractions were evaporated in vacuo to give a residue which was further purified using mass-directed preparative HPLC, to give the title compound as a colourless gum (0.018g).

LCMS (System A) R_t 2.12min Mass Spectrum *m/z* 230 [MH^+], 247[MNH_4^+]

Intermediate 40: [3-(Aminosulfonyl)phenyl]acetic acid compound with N,N,N-triethylamine (1:1)

A portion (0.120ml) of a solution of sodium hydroxide (0.123g) in water (3.05ml) was added to a stirred solution of Intermediate 39 (0.018g) in methanol (2ml) and water (1ml), and stirring was continued at 22°C for 7h. The pH of the mixture was adjusted to approximately 8, and the mixture was applied to an aminopropyl ion exchange cartridge (2g Isolute SPE, pre-conditioned with methanol). Elution with methanol (3 column volumes) followed by of 10% triethylamine in methanol (2 column volumes), and evaporation of the basic fractions in vacuo gave the title compound as a colourless gum (0.022g).

LCMS (System A) R_t 1.75min Mass Spectrum *m/z* 214 [MH^-], 233 [MNH_4^+]

Intermediate 41: 2-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1H-isoindole-1,3(2H)-dione

To a solution of 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (2g) in tetrahydrofuran (4 ml) was added 2-[(3,4-dichlorobenzyl)amino]ethanol (2.16 g) with stirring, under a nitrogen atmosphere. The mixture was heated to 66°C for 22h, then cooled to 0°C. A further portion of tetrahydrofuran (10 ml) was added, followed by triphenylphosphine (2.88 g). Diisopropyl azodicarboxylate (2.2 g) was then added over 10 min. The mixture was stirred at 0°C for a further 30 min, and at room temperature for 14h. To the crude solution was added ethyl acetate (100 ml), then 2M aqueous hydrochloric acid (250 ml). The resulting white precipitate was isolated by filtration, and dried in vacuo to give the title compound as its white crystalline hydrochoride salt (2.01g). This was partitioned between 8% aqueous sodium bicarbonate (200ml) and ethyl acetate (50ml). The organic phase was separated, dried over magnesium sulfate and the solvent evaporated in vacuo to give a solid. Dichloromethane (20ml) was

added to the residue and the solvent again evaporated in vacuo to give the title compound as a white solid (1.1g).

LC/MS R_t 2.91 min. Mass Spectrum *m/z* 405 [MH^+]

Intermediate 42: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2,2,2-trifluoroacetamide

To a stirred solution of Intermediate 19 (3.3g) in N,N-dimethylformamide (50ml) under nitrogen was added potassium carbonate (2.46g) and sodium iodide (2.12g). A solution of 3,4-dichlorobenzyl chloride (2ml) in N,N-dimethylformamide (10ml) was added dropwise to the mixture. The mixture was stirred at 22°C for 18h before the volatiles were removed in vacuo. The residue was partitioned between dichloromethane (100ml) and saturated aqueous sodium carbonate solution (50ml). The organic phase was subsequently washed with additional saturated aqueous sodium carbonate solution (2 x 50ml) and water (50ml) before drying over magnesium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 25% ethyl acetate in cyclohexane, to give the title compound as a colourless oil (2.97g).

LC/MS (System A) R_t 2.63 min, Mass Spectrum *m/z* 371 [MH^+].

Examples

Example 1: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-phenylacetamide

A mixture of Intermediate 1 (0.028g) and phenylacetic acid (0.015g) was treated with 1-methyl-2-pyrrolidinone (0.015ml) then heated in a 600W microwave oven, at full power, for 4min. The crude mixture was purified by chromatography on silica gel (Varian Bond-Elut, 1g) eluting with cyclohexane/ethyl acetate (4:1 followed by 2:1) to give the title compound as a colourless gum (0.029g).

LC-MS (System A): Rt 2.63min, Mass Spectrum *m/z* 393 [MH^+].

Example 2: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylsulfonyl)phenyl]acetamide salt with formic acid (1:1)

Example 2 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and [4-(methylsulfonyl)phenyl]acetic acid (0.043g) to give the title compound (0.03g).

LC-MS (System A): Rt 2.32mins, Mass Spectrum *m/z* 471 [MH^+].

Example 3: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(3-fluorophenyl)acetamide

Example 3 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (3-fluorophenyl)acetic acid (0.031g) to give the title compound (0.041g).

LC-MS (System A): Rt 2.65mins, Mass Spectrum *m/z* 411 [MH^+].

Example 4: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-fluorophenyl)acetamide

Example 4 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (4-fluorophenyl)acetic acid (0.031g) to give the title compound (0.019g).

LC-MS (System A): Rt 2.72mins, Mass Spectrum *m/z* 411 [MH^+].

Example 5: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylthio)phenyl]acetamide

Example 5 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and 4-(methylthio)phenylacetic acid (0.036g) to give the title compound (0.028g).

LC-MS (System A): Rt 2.77mins, Mass Spectrum *m/z* 439 [MH^+].

Example 6: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(3,4-difluorophenyl)acetamide

Example 6 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (3,4-difluorophenyl)acetic acid (0.034g) to give the title compound (0.0195g).

LC-MS (System A): Rt 2.84mins, Mass Spectrum *m/z* 429 [MH^+].

Example 7: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(dimethylamino)sulfonyl]phenyl}acetamide salt with formic acid (1:1)

Example 7 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and {4-[(dimethylamino)sulfonyl]phenyl}acetic acid (0.049g) to give the title compound (0.031g).

LC-MS (System A): Rt 2.46mins, Mass Spectrum *m/z* 500 [MH^+].

Example 8: 2-(3-Chlorophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide

Example 8 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (3-chlorophenyl)acetic acid (0.034g) to give the title compound (0.034g).

LC-MS (System A): Rt 2.64mins, Mass Spectrum *m/z* 427 [MH^+].

Example 9: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-methylphenyl)acetamide

Example 9 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (4-methylphenyl)acetic acid (0.03g) to give the title compound (0.024g).

LC-MS (System A): Rt 2.64mins, Mass Spectrum *m/z* 407 [MH^+].

Example 10: 4-[2-({[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide

Example 10 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and [4-(aminocarbonyl)phenyl]acetic acid (0.036g) to give the title compound (0.01g).

LC-MS (System A): Rt 2.20mins, Mass Spectrum *m/z* 436 [MH^+].

Example 11: 2-(4-Chlorophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide

Example 11 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.028g) and (4-chlorophenyl)acetic acid (0.019g) to give the title compound (0.033g).

LC-MS (System A): Rt 2.86min, Mass Spectrum *m/z* 427 [MH^+].

Example 12: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(dimethylamino)phenyl]acetamide salt with formic acid (1:1)

Example 12 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and [4-(dimethylamino)phenyl]acetic acid (0.036g) to give the title compound (0.025g).

LC-MS (System A): Rt 2.27mins, Mass Spectrum *m/z* 436 [MH^+].

Example 13: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,5-dichlorophenyl)acetamide

Example 13 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (2,5-dichlorophenyl)acetic acid (0.041g) to give the title compound (0.025g).

LC-MS (System A): Rt 2.89mins, Mass Spectrum *m/z* 463 [MH^+].

Example 14: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(trifluoromethyl)phenyl]acetamide

Example 14 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and [4-(trifluoromethyl)phenyl]acetic acid (0.041g) to give the title compound (0.015g).

LC-MS (System A): Rt 3.00mins, Mass Spectrum *m/z* 463 [MH^+].

Example 15: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(3,4-dichlorophenyl)acetamide

Example 15 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (3,4-dichlorophenyl)acetic acid (0.041g) to give the title compound (0.015g).

LC-MS (System A): Rt 2.93mins, Mass Spectrum *m/z* 461 [MH^+].

Example 16: 2-(2-Chlorophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide

Example 16 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (2-chlorophenyl)acetic acid (0.034g) to give the title compound (0.025g).

LC-MS (System A): Rt 2.67mins, Mass Spectrum *m/z* 429 [MH^+].

Example 17: 2-[3,5-Bis(trifluoromethyl)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide

Example 17 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and [3,5-bis(trifluoromethyl)phenyl]acetic acid (0.054g) to give the title compound (0.04g).

LC-MS (System A): Rt 3.24mins, Mass Spectrum *m/z* 529 [MH^+].

Example 18: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,4-dichlorophenyl)acetamide

Example 18 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (2,4-dichlorophenyl)acetic acid (0.041g) to give the title compound (0.019g).

LC-MS (System A): Rt 2.72mins, Mass Spectrum *m/z* 463 [MH^+].

Example 19: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-fluoro-2-methylphenyl)acetamide

Example 19 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (4-fluoro-2-methylphenyl)acetic acid (0.034g) to give the title compound (0.014g).

LC-MS (System A): Rt 2.77mins, Mass Spectrum *m/z* 425 [MH^+].

Example 20: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,6-dichlorophenyl)acetamide

Example 20 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and (2,6-dichlorophenyl)acetic acid (0.041g) to give the title compound (0.011g).

LC-MS (System A): Rt 2.81mins, Mass Spectrum *m/z* 463 [MH^+].

Example 21: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-phenoxyacetamide

Example 21 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.028g) and phenoxyacetic acid (0.017g) to give the title compound (0.026g).

LC-MS (System A): Rt 2.74min, Mass Spectrum *m/z* 409 [MH^+].

Example 22: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-methoxyphenyl)acetamide

Example 22 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.028g) and (4-methoxyphenyl)acetic acid (0.018g) to give the title compound (0.02g).

LC-MS (System A): Rt 2.66min, Mass Spectrum *m/z* 423 [MH^+].

Example 23: 2-(4-Chlorophenyl)-N-{[4-(3,4-dichlorobenzyl)-5,5-dimethylmorpholin-2-yl]methyl}acetamide

A mixture of Intermediate 3 (0.030g) and 4-chlorophenylacetic acid (0.020g) were treated with 1-methyl-2-pyrrolidinone (0.015ml) then heated in a 600W microwave oven, at full power, for 4min. The crude mixture was purified by chromatography on silica gel (Varian Bond-Elut cartridge, 1g) eluting with cyclohexane/ethyl acetate (19:1 followed by 1:1) to give a brown solid which was triturated with ether to give the title compound as an off-white solid (0.018g).

LC-MS (System A): Rt 3.21min, Mass Spectrum *m/z* 455 [MH^+].

Example 24: N-{[(*cis*)-4-(3,4-Dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}-2-phenylacetamide

A mixture of Intermediate 5 (0.060g) and phenylacetic acid (0.027g) was treated with 1-methyl-2-pyrrolidinone (0.015ml) then heated in a 600W microwave oven, at full power, for 4min. The crude mixture was purified by normal phase preparative HPLC to give the title compound as a colourless gum (27mg).

LC-MS (System A): Rt 2.85min, Mass Spectrum *m/z* 407 [MH^+].

Example 25: N-{[(*trans*)-4-(3,4-Dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}-2-phenylacetamide

Example 25 was prepared in an analogous manner to Example 24 using a mixture of Intermediate 5 (0.06g) and phenylacetic acid (0.027g) to give the title compound as a colourless gum (18mg).

LC-MS (System A): Rt 2.85min, Mass Spectrum *m/z* 407 [MH^+].

Example 26: 2-(4-Chlorophenyl)-N-{[(*cis*)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}acetamide

Example 26 was prepared in an analogous manner to Example 24 using a mixture of Intermediate 5 (0.06g) and (4-chlorophenyl)acetic acid (0.034g) to give the title compound (0.027g).

LC-MS (System A): Rt 3.10min, Mass Spectrum *m/z* 441 [MH^+].

Example 27: 2-(4-Chlorophenyl)-N-{[(*trans*)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}acetamide

Example 27 was prepared in an analogous manner to Example 24 using a mixture of Intermediate 5 (0.06g) and (4-chlorophenyl)acetic acid (0.034g) to give the title compound (0.018g).

LC-MS (System A): Rt 3.10min, Mass Spectrum *m/z* 441 [MH^+].

Example 28: N-({4-[3-(3,4-Dichlorophenyl)propyl]morpholin-2-yl}methyl)-2-phenylacetamide

A mixture of Intermediate 7 (0.030g) and phenylacetic acid (0.015g) was treated with 1-methyl-2-pyrrolidinone (0.015ml) then heated in a 600W microwave oven, at full power, for 4min. The crude mixture was purified by chromatography on silica gel (Varian Bond-Elut, 1g) eluting with cyclohexane/ethyl acetate (4:1 followed by 2:1) to give the title compound as a colourless gum (0.004g).

LC-MS (System A): Rt 2.74min, Mass Spectrum *m/z* 421 [MH^+].

Example 29: 2-(4-Chlorophenyl)-N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}acetamide trifluoroacetate

Intermediate 8 (0.060g) was dissolved in methanol (10ml) and loaded onto a solid phase extraction column (2g Isolute SCX sulphonic acid) which had been prepared by application of methanol. Elution with methanol, then 0.880 ammonia:methanol 10:90 gave a clear colourless gum (0.027g). This was treated with (4-chlorophenyl)acetic acid (0.017g) and N-methyl-2-pyrrolidinone (1 drop) and subjected to microwave irradiation (600W, full power, 4

min). Purification by automated preparative HPLC (gradient profile 30-60% (ii) over 20 mins, R_t 13 mins) gave the title compound (0.018g) as a white solid.

LC/MS (System A): R_t 2.87 min, Mass spectrum *m/z* 429 [MH^+].

Example 30: 1-(4-Chlorophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}cyclopropanecarboxamide trifluoroacetate

Example 30 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and 1-(4-chlorophenyl)cyclopropanecarboxylic acid (0.039g) to give the title compound (0.008g).

LC-MS (System A): Rt 3.03mins, Mass Spectrum *m/z* 455 [MH^+].

Example 31: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methoxy-2-methyl-1H-indol-3-yl)acetamide

Example 31 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and (5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (0.044g) to give the title compound (0.019g).

LC-MS (System A): Rt 2.63mins, Mass Spectrum *m/z* 476 [MH^+].

Example 32: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-thien-3-ylacetamide

Example 32 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and thien-3-ylacetic acid (0.028g) to give the title compound (0.016g).

LC-MS (System A): Rt 2.50mins, Mass Spectrum *m/z* 399 [MH^+].

Example 33: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

Example 33 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and (5-methyl-2-phenyl-1,3-oxazol-4-yl)acetic acid (0.043g) to give the title compound (0.036g).

LC-MS (System A): Rt 2.80mins, Mass Spectrum *m/z* 474 [MH^+].

Example 34: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide

Example 34 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and (5-methyl-1-phenyl-1H-pyrazol-4-yl)acetic acid (0.043g) to give the title compound (0.014g).

LC-MS (System A): Rt 2.61mins, Mass Spectrum *m/z* 473 [MH^+].

Example 35: 2-(4-Bromo-3,5-dimethyl-1H-pyrazol-1-yl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide

Example 35 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and (4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)acetic acid (0.047g) to give the title compound (0.032g).

LC-MS (System A): Rt 2.70mins, Mass Spectrum *m/z* 491 [MH^+].

Example 36: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-thiazol-4-yl)acetamide

Example 36 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and (2-phenyl-1,3-thiazol-4-yl)acetic acid (0.042g) to give the title compound (0.049g).

LC-MS (System A): Rt 2.85mins, Mass Spectrum *m/z* 476 [MH^+].

Example 37: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide

Example 37 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and (2-pyrazin-2-yl-1,3-thiazol-4-yl)acetic acid (0.044g) to give the title compound (0.05g).

LC-MS (System A): Rt 2.43mins, Mass Spectrum *m/z* 478 [MH^+].

Chiral analytical HPLC, eluent 60% EtOH/n-heptane: Rt 9.22min and 12.42 min.

Example 38: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-furyl)acetamide

Example 38 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.056g) and 2-furylacetic acid (0.025g) to give the title compound(0.044g).

LC-MS (System A): Rt 2.38mins, Mass Spectrum *m/z* 383 [MH^+].

Example 39: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylsulfonyl)phenyl]acetamide (single enantiomer of Example 2)

Example 39 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 9 (0.055g) and 4-(methylsulphonyl)phenylacetic acid (0.050g) to give the title compound (0.045g).

Chiral analytical HPLC, eluent 35% EtOH/n-heptane, Rt 20.56min

Example 40: N-{[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylsulfonyl)phenyl]acetamide

Example 40 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 10 (0.055g) and 4-(methylsulphonyl)phenylacetic acid (0.050g) to give the title compound (0.046g).

Chiral analytical HPLC, eluent 35% EtOH/n-heptane, Rt 17.16min

Example 41: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide

Intermediate 12 (0.050g) was treated with N,N-dimethylformamide (0.5ml) followed by 1-hydroxybenzotriazole hydrate (0.027g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.044g) and Intermediate 1 (0.042g) in N,N-dimethylformamide (0.5ml) and N,N-diisopropylethylamine (0.027ml). The mixture was stirred at 22°C for 20 h, then left to stand for 6 days. The solution was diluted with dichloromethane (10ml) and washed successively with dilute aqueous sodium hydrogen carbonate (10ml) and dilute aqueous sodium chloride (2 x 10ml). The organic phase was isolated using a hydrophobic frit (6ml) and drained directly onto an SCX column (2g Isolute SPE) which had been prepared by application of methanol. Elution with methanol, then .880 ammonia:methanol 10:90 gave the title compound (0.048g) as an orange glassy solid.

LC/MS (System A) Rt 2.93 min. Mass spectrum *m/z* 492 [MH^+].

Example 42: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide

Chiral separation from the racemic mixture of Example 37:

Example 37 was separated into its single enantiomers with a chiral preparative HPLC system. The separation was carried out using a Chiralpak AD column (2cm x 25cm), eluting with 60% ethanol in heptane (15ml/min over 25mins, UV detection λ = 215nm) to give the S isomer.

Chiral analytical HPLC, eluent 60% EtOH/n-heptane: Rt 12.22 min.

Example 43: N-{[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide

Example 43 was prepared in an analogous manner to Example 42 which similarly obtained the R isomer.

Chiral analytical HPLC, eluent 60% EtOH/n-heptane: Rt 9.20 min.

Example 44: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide

A solution of (5-phenyl-2H-tetraazol-2-yl)acetic acid (0.082g) in N,N-dimethylformamide (2ml) under nitrogen was treated with O-(7-azabenzotriazol-1-yl)-N,N,N'N'-tetramethylammonium hexafluorophosphate (0.152g) and N,N-diisopropylethylamine (0.139ml) followed by a solution of Intermediate 9 (0.110g) in N,N-dimethylformamide (3ml), and the mixture was stirred at 22°C for 4h. The solvent was removed in vacuo and the residue dissolved in ethyl acetate (20ml). The solution was washed with 10% aqueous citric

acid (20ml), brine (20ml), saturated aqueous sodium hydrogen carbonate (20ml) and brine (20ml), dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate, followed by trituration of the resultant product with diethyl ether, gave the title compound as a white solid (0.184g).

LC-MS (System A): Rt 2.85min. Mass Spectrum *m/z* 461 [MH^+].

Example 45: N-{[4-(3,4-Difluorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}acetamide

Example 45 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 24 (0.014g) and {4-[(methylsulfonyl)amino]phenyl}acetic acid (0.013g) to give the title compound (0.022g).

LC-MS (System A) Rt 2.09mins. Mass Spectrum *m/z* 454 [MH^+].

Example 46: N-{[(2S)-4-(4-Fluorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}acetamide

Example 46 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 24 (0.09g) and 4-(methylsulphonylamino)phenylacetic acid (0.1g) to give the title compound (0.077g).

LC-MS (System A) Rt 2.05mins. Mass Spectrum *m/z* 436 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 23.09 min.

Example 47: N-{[(2R)-4-(4-Fluorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}acetamide

Example 47 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 24 (0.023g) and 4-(methylsulphonylamino)phenylacetic acid (0.025g) to give the title compound (0.01g).

LC-MS (System A) Rt 2.06mins. Mass Spectrum *m/z* 436 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 18.78 min.

Example 48: N-{[4-(4-Fluorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}acetamide

Example 48 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 24 (0.013g) and 4-(methylsulphonylamino)phenylacetic acid (0.013g), with the exception that 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride and 1-hydroxybenzotriazole were used as the coupling reagents to give the title compound (0.019g).

LC-MS (System A) Rt 2.01mins Mass Spectrum *m/z* 436 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 19.40min and 23.51 min.

Example 49: N-({(2S)-4-[(5-Chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-{3-[(methylsulfonyl)amino]phenyl}acetamide

Example 49 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 14 (0.1g) and Intermediate 18 (0.1g) to give the title compound (0.102g).

LC-MS (System A) Rt 2.23mins. Mass Spectrum *m/z* 458 [MH^+].

Chiral analytical HPLC, eluent 20% EtOH/n-heptane: Rt 13.18 min.

Example 50: N-({(2R)-4-[(5-Chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-{3-[(methylsulfonyl)amino]phenyl}acetamide

Example 50 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 14A (0.1g) and Intermediate 18 (0.1g) to give the title compound (0.085g).

LC-MS (System A) Rt 2.27mins. Mass Spectrum *m/z* 458 [MH^+].

Chiral analytical HPLC, eluent 20% EtOH/n-heptane: Rt 10.65 min.

Example 51: N-({4-[(5-Chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-{3-[(methylsulfonyl)amino]phenyl}acetamide

Example 51 was prepared in an analogous manner to Example 44 using a mixture of Intermediate 24 (0.007g) and Intermediate 18 (0.007g) with the exception that 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride and 1-hydroxybenzotriazole were used as the coupling reagents to give the title compound (0.0077g).

LC-MS (System A) Rt 2.29mins. Mass Spectrum *m/z* 458 [MH^+].

Chiral analytical HPLC, eluent 20% EtOH/n-heptane: Rt 10.67min and 13.23 min.

Example 52: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,6-difluorophenyl)acetamide

Example 52 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 1 (0.055g) and 2,6-difluorophenylacetic acid (0.035g) to give thetitle compound (0.057g).

LC-MS (System A) Rt 2.70mins. Mass Spectrum *m/z* 429 [MH^+].

Example 53: N-Cyclopropyl-3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide

A mixture of Example 57 (0.300g), 1-hydroxybenzotriazole (0.171g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.098g) was stirred in N,N-dimethylformamide (6.6ml) and N,N-diisopropylethylamine (0.190ml) was added. The mixture was stirred at 20°C until a clear solution was obtained. A portion of the mixture (1.1ml) was transferred into a flask, cyclopropylamine (0.0077ml) was added, and the mixture was stirred at 20°C under nitrogen for 17h. Polystyrene methylisocyanate (Argonaut

Technologies, 0.034g, loading 1.57mmol/g) and macroporous triethylammonium methylpolystyrene carbonate (Argonaut Technologies, 0.015g, loading 3.2mmol/g) were added, and stirring was continued for 1h. The mixture was filtered, the resin beads washed with methanol and the combined filtrates reduced in volume to approximately 1ml and purified by solid phase extraction (2g SCX cartridge), eluting with methanol followed by 10% 0.880 ammonia in methanol. The product was isolated by evaporation of the solvent from the basic fraction and was further purified by solid phase extraction (5g Varian Bondelut silica gel cartridge), eluting successively with one column volume of dichloromethane, chloroform, ether, ethylacetate, acetone, acetonitrile and methanol, to give the title compound as a colourless gum (0.034g).

LCMS (system A) R_t 2.65min. Mass Spectrum *m/z* 476, 478 [MH^+].

Example 54: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

Intermediate 16 (0.077g) in anhydrous N,N-dimethylformamide (2ml) was treated with N,N-diisopropylethylamine (0.044ml) and 3,4-dichlorobenzyl chloride (0.035ml). The mixture was stirred at 22°C for 19h, and partitioned between chloroform (15ml) and saturated aqueous sodium bicarbonate (15ml). The phases were separated using a hydrophobic frit and the organic phase loaded onto a solid phase extraction column (10g SCX). Elution with methanol, then .880 ammonia:methanol 10:90 gave a clear colourless gum. The crude mixture was purified by flash chromatography on silica gel (Trikonex Flashtube™ 2008, 8g), eluting with ethyl acetate, to give the title compound as a colourless gum (0.0023g).

LC/MS (System A) R_t 2.88 min. Mass spectrum *m/z* 474 [MH^+].

Chiral analytical HPLC, eluent 10% EtOH/n-heptane, R_t 12.39 min.

Example 54 (Alternative Procedure): N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

Example 54 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 9 (0.055g) and 2-phenyl-5-methyl-4-oxazolylacetic acid (0.050g) to give the title compound (0.046g).

LC-MS (System A) Rt 2.88mins. Mass Spectrum *m/z* 474 [MH^+].

Example 55: N-{[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

Example 55 was prepared in an analogous manner to that described in Example 54 using Intermediate 17 (0.081g) and 3,4-dichlorobenzyl chloride (0.037ml) to give a colourless gum (0.011g).

LC/MS (System A) R_t 2.87 min. Mass spectrum *m/z* 474 [MH^+].

Chiral analytical HPLC, eluent 10% EtOH/n-heptane, R_t 9.812 min.

Example 55 (Alternative Procedure): N-{[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide

Example 55 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 10 (0.055g) and 2-phenyl-5-methyl-4-oxazolylacetic acid (0.050g) to give the title compound (0.042g).

LC-MS (System A) Rt 2.88mins. Mass Spectrum *m/z* 474 [MH^+].

A mixture of Examples 54 and 55: Chiral analytical HPLC, eluent 10% EtOH/n-heptane, R_t 9.73 and 12.42min.

Example 56: Methyl 3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzoate

A mixture of [3-(methoxycarbonyl)phenyl]acetic acid (0.200g), Intermediate 1 (0.284g), 1-hydroxybenzotriazole (0.182g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.316g) was stirred in dichloromethane (10ml), and N,N-diisopropylethylamine (0.352ml) was added to the solution. Stirring at 20°C under nitrogen was continued for 8h. The mixture was purified by solid phase extraction (2x10g Varian Bondelut silica gel cartridges), eluting successively with one column volume of dichloromethane, chloroform, ether, ethyl acetate, acetone, acetonitrile and methanol, to give the title compound as a colourless gum, (0.266g).

LCMS (system A) R_t 2.70min. Mass Spectrum *m/z* =451, 453 [MH^+].

Example 57: 3-[2-({[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzoic acid compound with N,N,N-triethylamine (1:1)

To a solution of Example 56 (0.261g) in a mixture of water (4ml) and methanol (12ml) was added a solution of sodium hydroxide (0.054g) in water (0.5ml) and the mixture was stirred at 20°C for 72h. The pH of the mixture was adjusted to approximately 6 by the addition of 2N hydrochloric acid and the mixture was purified by solid phase extraction (10g SCX cartridge), eluting with methanol followed by 10% triethylamine in methanol. Evaporation of the basic fraction in vacuo gave the title compound as a colourless gum, (0.319g).

LCMS (system A) R_t 2.66min. Mass Spectrum *m/z* 437, 439 [MH^+].

Examples 58-85

	Name	Preparation analogous to	Characterising Data
58	2-[3-(acetylamino)phenyl]-N-{[4-	Example 1	LC-MS (System A):

	(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide		Rt 2.33mins. Mass Spectrum *m/z* 450 [MH$^+$].
59	2-(3-acetyl-1-benzothien-4-yl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide trifluoroacetate	Example 1	LC-MS (System A): Rt 2.90mins. Mass Spectrum *m/z* 491 [MH$^+$].
60	2-(5-bromopyridin-3-yl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide compound with formic acid (1:1)	Example 1	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 474 [MH$^+$].
61	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,3-dimethylquinoxalin-6-yl)acetamide	Example 1	LC-MS (System A): Rt 2.51mins. Mass Spectrum *m/z* 473 [MH$^+$].
62	2-(4-acetylphenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide trifluoroacetate	Example 1	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 435 [MH$^+$].
63	2-(4-acetylphenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 435 [MH$^+$].
64	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-isobutyrylphenyl)acetamide trifluoroacetate	Example 1	LC-MS (System A): Rt 2.84mins. Mass Spectrum *m/z* 463 [MH$^+$].
65	methyl 4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzoate trifluoroacetate	Example 1	LC-MS (System A): Rt 2.65mins. Mass Spectrum *m/z* 451 [MH$^+$].
66	methyl 4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-	Example 56	LC-MS (System A): Rt 2.73mins.

	yl]methyl}amino)-2-oxoethyl]benzoate		Mass Spectrum *m/z* 451 [MH$^+$].
67	2-(4-cyanophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide trifluoroacetate	Example 1	LC-MS (System A): Rt 2.60mins. Mass Spectrum *m/z* 418 [MH$^+$].
68	2-(4-cyanophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.63mins. Mass Spectrum *m/z* 418 [MH$^+$].
69	N-{[(2S,5R)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}-2-phenylacetamide	Example 24 from (2R)-2-aminopropan-1-ol	LC-MS (System A): Rt 2.88mins. Mass Spectrum *m/z* 407 [MH$^+$].
70	2-(4-chlorophenyl)-N-{[(2S,5R)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}acetamide	Example 24	LC-MS (System A): Rt 3.13 mins. Mass Spectrum *m/z* 441 [MH$^+$].
71	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(3-fluoro-4-hydroxyphenyl)acetamide trifluoroacetate	Example 1	LC-MS (System A): Rt 2.66mins. Mass Spectrum *m/z* 427 [MH$^+$].
72	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-furyl)acetamide	Example 42	LC-MS (System A): Rt 2.38mins. Mass Spectrum *m/z* 383 [MH$^+$]. Chiral Analytical HPLC Eluent 20% EtOH/heptane Rt 9.97mins.
73	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}acetamide	Example 53	LC-MS (System A): Rt 2.25mins. Mass Spectrum *m/z* 519 [MH$^+$].

74	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-[2-(dimethylamino)ethyl]benzamide	Example 53	LC-MS (System A): Rt 2.13mins. Mass Spectrum *m/z* 507 [MH^+].
75	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N,N-dimethylbenzamide	Example 53	LC-MS (System A): Rt 2.53mins. Mass Spectrum *m/z* 464 [MH^+].
76	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-ethylbenzamide	Example 53	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 464 [MH^+].
77	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-(2-hydroxyethyl)benzamide	Example 53	LC-MS (System A): Rt 2.28mins. Mass Spectrum *m/z* 480 [MH^+].
78	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(morpholin-4-ylcarbonyl)phenyl]acetamide	Example 53	LC-MS (System A): Rt 2.45mins. Mass Spectrum *m/z* 506 [MH^+].
79	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{3-[(dimethylamino)sulfonyl]phenyl} acetamide	Example 162	LC-MS (System A): Rt 2.66mins. Mass Spectrum *m/z* 500 [MH^+].
80	N-{[(2R)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(dimethylamino)sulfonyl]phenyl} acetamide	Example 42	LC-MS (System A): Rt 2.81mins. Mass Spectrum *m/z* 500 [MH^+]. Chiral Analytical HPLC Eluent 40% EtOH/heptane Rt 13.10min.
81	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-	Example 162	LC-MS (System A): Rt mins 2.62.

	yl]methyl}-2-{4-[(dimethylamino)sulfonyl]phenyl} acetamide		Mass Spectrum *m/z* 500 [MH$^+$].
82	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-methylbenzamide	Example 53	LC-MS (System A): Rt 2.49mins. Mass Spectrum *m/z* 450 [MH$^+$].
83	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-isopropylbenzamide	Example 53	LC-MS (System A): Rt 2.69mins. Mass Spectrum *m/z* 478 [MH$^+$].
84	N-cyclopropyl-4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide	Example 53	LC-MS (System A): Rt 2.61mins. Mass Spectrum *m/z* 476 [MH$^+$].
85	4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-(2-methoxyethyl)benzamide	Example 53	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 494 [MH$^+$].

Example 86: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide

2-(3,5–Dimethoxy–4–formylphenoxy)ethoxymethyl polystyrene resin (Novabiochem, loading 0.9mmol/g, 1g) was swollen with the minimum quantity of 1% acetic acid/N,N-dimethylformamide to form a slurry. Intermediate 1 (0.969g) was added to this mixture in N,N-dimethylformamide (2ml) and the mixture shaken at room temperature for 100 min. 1% Acetic acid/N,N-dimethylformamide (10ml) was added followed by sodium triacetoxyborohydride (333mg). The mixture was then shaken for 20 min before further sodium triacetoxyborohydride (0.300g) was added, and shaking was continued at room temperature for 18 h. The reaction solution was then drained off and the resin washed with (N,N-dimethylformamide: 5 x 10ml, methanol: 5 x 10ml, dichloromethane: 5 x 10ml, diethyl ether: 3 x 10ml). The resin was then dried in vacuo.

The resin (0.100g) was then swollen with dichloromethane, and excess solvent drained off. A solution of diisopropylcarbodiimide (0.0705ml) and bromo acetic acid (0.125g) in 1:1 dichloromethane/dimethyl formamide (1ml), was made and stirred for ca. 5 min, before

adding to the resin. The resin was then shaken at room temperature for 2 h. The solution was drained off and the resin washed with (N,N-dimethylformamide: 5 x 10ml, methanol: 5 x 10ml, dichloromethane: 5 x 10ml).

A solution of potassium tert–butoxide (0.050g) and the azole 5-phenyl-1-H-tetrazole (0.131g) in N,N-dimethylformamide (1ml) was prepared and stirred for 5 min before this was added to the resin. The reaction mixture was heated to 60°C and shaken for 18 h. The reaction solution was then drained off and the resin washed with (N,N-dimethylformamide: 5 x 1ml, methanol: 5 x 1ml, dichloromethane: 5 x 1ml).

1:1 trifluoroacetic acid/dichloromethane solution (1ml) was then added to the resin, and the mixture shaken for 90 min. The resin was filtered off, washed with dichloromethane (1ml), and the combined filtrate and washings evaporated. The resulting solid was purified by mass directed preparative HPLC to give the title compound (15 mg).

LC-MS (System A) R_t 2.77 min. Mass Spectrum *m/z* 461 [MH^+].

Examples 87-90

	Name	Preparation analogous to	Characterising Data
87	2-(4-bromo-1H-imidazol-1-yl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 86	LC-MS (System A): Rt 2.34mins. Mass Spectrum *m/z* 462 [MH^+].
88	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-nitrophenyl)acetamide	Example 56	LC-MS (System A): Rt 2.92mins. Mass Spectrum *m/z* 438 [MH^+].
89	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(3-nitrophenyl)acetamide	Example 56	LC-MS (System A): Rt mins 2.92. Mass Spectrum *m/z* 438 [MH^+].
90	2-[3-(acetylamino)phenyl]-N-{[4-(3-fluorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.13mins. Mass Spectrum *m/z* 400 [MH^+].

Example 91: N-{[4-(3-fluorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}acetamide

A mixture of Intermediate 29 (0.0134g), {4-[(methylsulfonyl)amino]phenyl}acetic acid (0.0137g, known compound WO 9929655 A1), 1-hydroxybenzotriazole (0.0097g) and N,N-diisopropylethylamine (0.01ml) in N,N-dimethylformamide (0.5ml) was treated with a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.00138g) in N,N-dimethylformamide (0.5ml). The mixture was stirred at 20°C for 24h. The mixture was partitioned between dichloromethane (4ml) and saturated aqueous sodium hydrogen carbonate (4ml). The phases were separated and the organic phase applied to an ion exchange cartridge (2g Isolute SCX, prewashed with methanol). The SCX cartridge was eluted with methanol (10ml) followed by 10% 0.880 ammonia in methanol (10ml) and the appropriate fractions were concentrated in vacuo to give the title compound as a colourless gum (0.0174g).

LCMS (system A) R_t 2.14min. Mass Spectrum *m/z* 436 [MH^+].

Examples 92-134

	Name	Preparation analogous to	Characterising Data
92	2-[3-(acetylamino)phenyl]-N-{[4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.31mins. Mass Spectrum *m/z* 418 [MH^+].
93	2-[4-(acetylamino)phenyl]-N-{[4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.10mins. Mass Spectrum *m/z* 418 [MH^+].
94	N-{[4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 91	LC-MS (System A): Rt 2.09mins. Mass Spectrum *m/z* 554 [MH^+].
95	N-{[4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}-2-{3-[(methylsulfonyl)amino]phenyl} acetamide	Example 91	LC-MS (System A): Rt 2.13mins. Mass Spectrum *m/z* 446 [MH^+].
96	N-{[4-(3,4-difluorobenzyl)morpholin-2-	Example 91	LC-MS (System A): Rt 2.04mins.

	yl]methyl}-2-[3-(methylsulfonyl)phenyl]acetamide		Mass Spectrum *m/z* 439 [MH$^+$].
97	N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylsulfonyl)phenyl]acetamide	Example 91	LC-MS (System A): Rt 2.09mins. Mass Spectrum *m/z* 437 [MH$^+$].
98	N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-[3-(methylsulfonyl)phenyl]acetamide	Example 91	LC-MS (System A): Rt 2.11mins. Mass Spectrum *m/z* 437 [MH$^+$].
99	2-[3-(acetylamino)phenyl]-N-{[4-(4-fluorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 1.95mins. Mass Spectrum *m/z* 400 [MH$^+$].
100	2-[4-(acetylamino)phenyl]-N-{[4-(4-fluorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 1.91mins. Mass Spectrum *m/z* 400 [MH$^+$].
101	N-{[4-(4-fluorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 91	LC-MS (System A): Rt 2.10mins. Mass Spectrum *m/z* 428 [MH$^+$].
102	N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylsulfonyl)phenyl]acetamide	Example 91	LC-MS (System A): Rt 2.36mins. Mass Spectrum *m/z* 471 [MH$^+$].
103	2-[3-(acetylamino)phenyl]-N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.30mins. Mass Spectrum *m/z* 450 [MH$^+$].
104	N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}	Example 91	LC-MS (System A): Rt 2.37mins. Mass Spectrum *m/z* 486 [MH$^+$].

	acetamide		
105	N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-{[(methylamino)carbonyl]amino}phenyl)acetamide	Example 91	LC-MS (System A): Rt 2.24mins. Mass Spectrum *m/z* 465 [MH^+].
106	N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 91	LC-MS (System A): Rt 2.44mins. Mass Spectrum *m/z* 478 [MH^+].
107	N-({4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-[4-(methylsulfonyl)phenyl]acetamide	Example 91	LC-MS (System A): Rt 2.16mins. Mass Spectrum *m/z* 443 [MH^+].
108	2-[3-(acetylamino)phenyl]-N-({4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)acetamide	Example 91	LC-MS (System A): Rt 2.13mins. Mass Spectrum *m/z* 422 [MH^+].
109	N-({4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-{4-[(methylsulfonyl)amino]phenyl}acetamide	Example 91	LC-MS (System A): Rt 2.18mins. Mass Spectrum *m/z* 458 [MH^+].
110	N-({4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 91	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 450 [MH^+].
111	2-[3-(acetylamino)phenyl]-N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.37mins. Mass Spectrum *m/z* 416 [MH^+].
112	N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl}acetamide	Example 91	LC-MS (System A): Rt 2.37mins. Mass Spectrum *m/z* 452 [MH^+].

113	2-[4-(acetylamino)phenyl]-N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.31mins. Mass Spectrum *m/z* 416 [MH^+].
114	N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-(4-{[(methylamino)carbonyl]amino}phenyl)acetamide	Example 91	LC-MS (System A): Rt 2.31mins. Mass Spectrum *m/z* 431 [MH^+].
115	N-{[4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-(2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 91	LC-MS (System A): Rt 2.46 mins. Mass Spectrum *m/z* 444 [MH^+].
116	2-[4-(acetylamino)phenyl]-N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 91	LC-MS (System A): Rt 2.51mins. Mass Spectrum *m/z* 450 [MH^+].
117	N-{[4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-[3-(methylsulfonyl)phenyl]acetamide	Example 91	LC-MS (System A): Rt 2.43mins. Mass Spectrum *m/z* 471 [MH^+].
118	2-[4-(aminosulfonyl)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.37mins. Mass Spectrum *m/z* 472 [MH^+].
119	2-[2-(acetylamino)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.44mins. Mass Spectrum *m/z* 450 [MH^+].
120	2-(3-cyanophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.64mins. Mass Spectrum *m/z* 418 [MH^+].
121	N-{[(2S,5R)-4-(2,5-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}-2-	Example 24	LC-MS (System A): Rt 2.73 mins.

	phenylacetamide		Mass Spectrum *m/z* 407 [MH^+].
122	2-(4-chlorophenyl)-N-{[(2S,5R)-4-(2,5-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}acetamide	Example 24	LC-MS (System A): Rt 3.02 mins. Mass Spectrum *m/z* 441 [MH^+].
123	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-fluorophenyl)acetamide	Example 1	LC-MS (System A): Rt 2.67 mins. Mass Spectrum *m/z* 411 [MH^+].
124	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,3-difluorophenyl)acetamide	Example 1	LC-MS (System A): Rt 2.75 mins. Mass Spectrum *m/z* 429 [MH^+].
125	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,4-difluorophenyl)acetamide	Example 1	LC-MS (System A): Rt 2.74 mins. Mass Spectrum *m/z* 429 [MH^+].
126	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2,5-difluorophenyl)acetamide	Example 1	LC-MS (System A): Rt 2.73 mins. Mass Spectrum *m/z* 429 [MH^+].
127	3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-(2-methoxyethyl)benzamide	Example 53	LC-MS (System A): Rt mins 2.57. Mass Spectrum *m/z* 494 [MH^+].
128	3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-ethylbenzamide	Example 53	LC-MS (System A): Rt mins 2.65. Mass Spectrum *m/z* 464 [MH^+].
129	3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N,N-dimethylbenzamide	Example 53	LC-MS (System A): Rt 2.61mins. Mass Spectrum *m/z* 464 [MH^+].

130	3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-[2-(dimethylamino)ethyl]benzamide	Example 53	LC-MS (System A): Rt 2.27mins. Mass Spectrum *m/z* 507 [MH^+].
131	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}acetamide	Example 53	LC-MS (System A): Rt 2.25mins. Mass Spectrum *m/z* 519 [MH^+].
132	2-(3-aminophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 56	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 408 [MH^+].
133	2-(4-aminophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 56	LC-MS (System A): Rt 2.29mins. Mass Spectrum *m/z* 408 [MH^+].
134	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide hydrochloride	Example 54	LC-MS (System A): Rt 2.90 mins. Mass Spectrum *m/z* 474 [MH^+].

Example 135: N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide fumarate salt

Example 54 (1g) was dissolved in acetonitrile (10ml) and methanol (3ml). Fumaric acid (0.245g) was added forming a slurry. The slurry was heated to and held at reflux for 1h, during which time the reaction mixture became a solution. After 1h heating, the solution was allowed to cool slowly to 23°C. Product was filtered off and washed with acetonitrile (2x 5ml), then dried in a vacuum oven at 50°C for 16h, to give the title compound as a white solid (0.35g).

^{1}H nmr (400MHz, d_6 DMSO) 13δ(2H, v.br.s, fumaric acid COOH), 8.03δ(1H, br.t, NH), 7.92-7.87δ(2H, m, aromatic CH's), 7.56δ(1H, d, aromatic CH), 7.52-7.46δ(4H, m, aromatic CH's), 7.27δ(1H, dd, aromatic CH), 6.62δ(2H, s, fumaric acid CH), 3.78δ(1H, ddd, CH), 3.53-3.44δ(2H, m, 2xCH), 3.43δ(2H, s, CH_2), 3.35δ(2H, s, CH_2), 3.12δ(2H, br.t, CH_2), 2.68δ(1H, br. dd, CH), 2.56δ(1H, dddd, CH), 2.31δ(3H, s, CH_3), 2.05δ(1H, ddd, CH), 1.82δ(1H, dd, CH).

Examples 136-138

	Name	Preparation analogous to	Characterising Data
136	2-[4-(acetylamino)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 139	LC-MS (System A): Rt mins 2.49. Mass Spectrum *m/z* 450 [MH^+].
137	N-{4-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]phenyl}-2-methylpropanamide	Example 139	LC-MS (System A): Rt 2.77mins. Mass Spectrum *m/z* 478 [MH^+].
138	N-{3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]phenyl}-2-methylpropanamide	Example 139	LC-MS (System A): Rt 2.77mins. Mass Spectrum *m/z* 478 [MH^+].

Example 139: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{3-[(methylsulfonyl)amino]phenyl}acetamide

Methanesulphonylchloride (0.022ml) was added to a stirred solution of Example 132 (0.114g) in dichloromethane (5ml), and stirring was continued at 22°C for 2h. After leaving to stand for a further 112h, tris-(2-aminoethyl)amine polystyrene resin (0.026g) was added and stirring continued for a further 2h. N,N-Dimethylformamide (1ml) was added and the mixture applied to a 10g ion exchange cartridge (Isolute SCX, pre-conditioned with methanol). Elution with methanol (3 column volumes) followed by 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the first basic fraction gave a residue, which was re-dissolved in dichloromethane, treated with polystyrene methylisocyanate resin (3.85mmol/g, 0.026g), and left to stand for 1h. The mixture was applied to a 10g silica gel cartridge (Varian Bond Elut, pre-conditioned with dichloromethane), and eluted with 1 column volume each of dichloromethane, chloroform, ether, ethyl acetate, acetone, acetonitrile and methanol. The appropriate fraction was evaporated in vacuo to give the title compound as a colourless gum (0.115g).

LC/MS (system A) R_t 2.65min Mass Spectrum *m/z* 486 [MH^+]

Examples 140-150

	Name	Preparation analogous to	Characterising Data
140	N-{[(2S,5R)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	Example 24	LC-MS (System A): Rt 2.93mins. Mass Spectrum *m/z* 488 [MH^+]. Normal Phase Analytical HPLC RT 14.31 mins.
141	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylsulfonyl)amino]phenyl} acetamide	Example 139	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 486 [MH^+].
142	N-{3-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]phenyl}-2-(dimethylamino)acetamide	Example 136	LC-MS (System A): Rt 2.29mins. Mass Spectrum *m/z* 493 [MH^+].
143	2-{4-[bis(methylsulfonyl)amino]phenyl}-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 139	LC-MS (System A): Rt 2.62mins. Mass Spectrum *m/z* 564, 566 [MH^+].
144	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 3.05mins. Mass Spectrum *m/z* 490 [MH^+].
145	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.60mins. Mass Spectrum *m/z* 492 [MH^+].
146	N-{[4-(3,4-dichlorobenzyl)morpholin-2-	Example 56	LC-MS (System A): Rt 2.61mins.

	yl]methyl}-2-[3-(methylsulfonyl)phenyl]acetamide		Mass Spectrum *m/z* 471 [MH^+].
147	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[4-(methylsulfonyl)-2-nitrophenyl]acetamide	Example 41	LC-MS (System A): Rt 2.6mins. Mass Spectrum *m/z* 518 [MH^+].
148	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-hydroxyphenyl)acetamide	Example 41	LC-MS (System A): Rt 2.52mins. Mass Spectrum *m/z* 409 [MH^+].
149	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.78mins. Mass Spectrum *m/z* 460 [MH^+].
150	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[methyl(methylsulfonyl)amino]phenyl}acetamide	Example 151	LC-MS (System A): Rt 2.73mins. Mass Spectrum *m/z* 500 [MH^+].

Example 151: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{3-[methyl(methylsulfonyl)amino]phenyl}acetamide

Potassium carbonate (0.035g) and iodomethane (0.015ml) were added to a stirred solution of Example 139 (0.115g) in acetone (1ml), and stirring was continued at 22°C for 72h before a further portion of iodomethane (0.003ml) was added. After stirring for a further 24h, more iodomethane (0.003ml) and potassium carbonate (0.007g) were added, and the mixture stirred for a further 48h. The mixture was applied in two equal portions to two ion exchange cartridges (2g Isolute SCX, pre-conditioned with methanol). Elution with methanol (3 column volumes) followed by 10% 0.880 ammonia in methanol (2 column volumes), and evaporation of the first basic fraction from each elution in vacuo gave the title compound as a pale yellow gum (0.038g).

LC/MS (system A) R_t 2.73min Mass Spectrum *m/z* 500 [MH^+]

Examples 152-157

	Name	Preparation analogous to	Characterising Data

152	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-4-(methylsulfonyl)butanamide	Example 44	LC-MS (System A): Rt 2.18mins. Mass Spectrum *m/z* 423 [MH^+]
153	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[5-methyl-2-(5-methylthien-2-yl)-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.87mins. Mass Spectrum *m/z* 494 [MH^+].
154	2-[2-amino-4-(methylsulfonyl)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.36mins. Mass Spectrum *m/z* 486 [MH^+].
155	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-thien-2-yl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.79mins. Mass Spectrum *m/z* 480 [MH^+].
156	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(2-furyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.64mins. Mass Spectrum *m/z* 464 [MH^+].
157	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}pent-4-ynamide	Example 1	LC-MS (System A): Rt 2.30mins. Mass Spectrum *m/z* 355 [MH^+].

Example 158: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-pyridin-3-yl-1,3-oxazol-4-yl)acetamide compound with formic acid (1:1)

N,N'-carbonyldiimidazole (15mg) was added to a stirred solution of Intermediate 34 (20mg) at 22°C under nitrogen, and the mixture was stirred at 22°C for 1h. Intermediate 9 (26mg) was added and the mixture stirred at 22°C for 24h. The mixture was applied directly to a sulphonic acid ion exchange cartridge (Isolute SCX, 2g) and eluted with methanol followed by 10% 0.880 ammonia in methanol. Evaporation of the methanolic ammonia fraction gave a gum (50mg) which was further purified by solid phase extraction on silica gel (1g Varian Bondelut cartridge), eluting with chloroform, ether, ethyl acetate, acetone and

methanol to give a gum (38mg). The gum was partitioned between dichloromethane and water, and the organic layer treated with polystyrene methylisocyanate resin (Argonaut, 95mg, 1.6mmol/g). After shaking for 4h the resin was filtered off and the filtrate evaporated to give a gum (29mg), which was further purified by chromatography on silica gel, eluting with dichloromethane: ethanol : 0.880 ammonia 100:0:0 - 95:5:0.5, followed by mass directed preparative HPLC to give the title compound (7.6mg).

LC-MS (System A) Rt 2.48min. Mass Spectrum *m/z* 475 [MH^+].

Examples 159-161

	Name	Preparation analogous to	Characterising Data
159	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-isopropyl-5-methyl-1,3-oxazol-4-yl)acetamide	Example 158	LC-MS (System A): Rt 2.66mins. Mass Spectrum *m/z* 440 [MH^+].
160	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(methylamino)sulfonyl]phenyl} acetamide	Example 162	LC-MS (System A): Rt 2.50mins. Mass Spectrum *m/z* 486 [MH^+].
161	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{4-[(ethylamino)sulfonyl]phenyl} acetamide	Example 162	LC-MS (System A): Rt 2.58mins. Mass Spectrum *m/z* 500 [MH^+].

Example 162: 2-[3-(Aminosulfonyl)phenyl]-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide

To a stirred solution of Intermediate 40 (0.021g) in N,N-dimethylformamide (1ml) was added 1-hydroxybenzotriazole (0.015g), N,N-diisopropylethylamine (0.028ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.025g) followed by a solution of Intermediate 9 (0.023g) in N,N-dimethylformamide (1ml). The mixture was stirred for 4h at 22°C, and applied to an ion exchange cartridge (2g Isolute SCX, pre-conditioned with methanol). Elution with methanol (3 column volumes) followed 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the first basic fraction in vacuo gave a residue which was re-dissolved in dichloromethane and applied to a silica gel cartridge (2g

Varian Bond Elut, pre-conditioned with dichloromethane). Elution with dichloromethane, chloroform, ether, ethyl acetate, acetone, acetonitrile and methanol (1 column volume each), and evaporation of the product containing fractions in vacuo gave the title compoundas a yellow gum (0.026g).

LCMS (System A) R_t 2.38min Mass Spectrum *m/z* 472 [MH^+].

Chiral Analytical HPLC on Chiralcel OD-H column, detection at 230nm, eluent 25% EtOH/ n-heptane, Rt 12.4min.

Examples 162A-213

	Name	Preparation analogous to	Characterising Data
162 A	2-[3-(Aminosulfonyl)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 162 (from Intermediate 1)	LC-MS (System A): Rt 2.36mins. Mass Spectrum *m/z* 472 [MH^+]. Chiral Analytical HPLC on Chiralcel OD-H column, detection at 230nm, eluent 25% EtOH/ n-heptane, Rt 12.5min and 10.3min.
163	2-{3-[(cyclopropylamino)sulfonyl]phenyl}-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 162	LC-MS (System A): Rt 2.66mins. Mass Spectrum *m/z* 512 [MH^+].
164	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{3-[(ethylamino)sulfonyl]phenyl} acetamide	Example 162	LC-MS (System A): Rt 2.62mins. Mass Spectrum *m/z* 500 [MH^+].
165	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{3-[(methylamino)sulfonyl]phenyl} acetamide	Example 162	LC-MS (System A): Rt 2.50mins. Mass Spectrum *m/z* 486 [MH^+].

166	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-morpholin-4-yl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.41mins. Mass Spectrum *m/z* 483 [MH^+].
167	2-[4-(aminosulfonyl)phenyl]-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 162	LC-MS (System A): Rt 2.34mins. Mass Spectrum *m/z* 472 [MH^+].
168	2-{4-[(cyclopropylamino)sulfonyl]phenyl}-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 162	LC-MS (System A): Rt 2.65mins. Mass Spectrum *m/z* 512 [MH^+].
169	methyl 2-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-2H-1,2,3-benzotriazole-5-carboxylate	Example 86	LC-MS (System A): Rt 2.76mins. Mass Spectrum *m/z* 492 [MH^+].
170	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)acetamide	Example 86	LC-MS (System A): Rt 2.59mins. Mass Spectrum *m/z* 433 [MH^+].
171	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-pyridin-2-yl-2H-tetraazol-2-yl)acetamide	Example 86	LC-MS (System A): Rt 2.48mins. Mass Spectrum *m/z* 462 [MH^+].
172	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-pyridin-3-yl-2H-tetraazol-2-yl)acetamide	Example 86	LC-MS (System A): Rt 2.45mins. Mass Spectrum *m/z* 462 [MH^+].
173	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[5-(3-formylphenyl)-2H-tetraazol-2-yl]acetamide	Example 86	LC-MS (System A): Rt 2.77mins. Mass Spectrum *m/z* 489 [MH^+].

174	methyl 1-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-1H-1,2,3-benzotriazole-5-carboxylate, compound with methyl 1-[2-({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-1H-1,2,3-benzotriazole-6-carboxylate (1:1)	Example 86	LC-MS (System A): Rt 2.66mins. Mass Spectrum *m/z* 492 [MH^+].
175	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(2-furyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.65mins. Mass Spectrum *m/z* 464 [MH^+].
176	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-thien-2-yl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.80mins. Mass Spectrum *m/z* 478 [MH^+].
177	N-({(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.75mins. Mass Spectrum *m/z* 446 [MH^+].
178	N-{[(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.97mins. Mass Spectrum *m/z* 474 [MH^+].
179	N-({(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.82mins. Mass Spectrum *m/z* 464 [MH^+].
180	N-{[(2S)-4-(4-fluorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.54mins. Mass Spectrum *m/z* 442 [MH^+].
181	N-{[(2S)-4-(2,3-	Example 54	LC-MS (System A):

	dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide		Rt 2.97mins. Mass Spectrum *m/z* 492 [MH^+].
182	N-({(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-2-(2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.64mins. Mass Spectrum *m/z* 432 [MH^+].
183	N-{[(2S)-4-(4-fluorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.39mins. Mass Spectrum *m/z* 410 [MH^+].
184	N-{[(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.86mins. Mass Spectrum *m/z* 460 [MH^+].
185	N-{[(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.59mins. Mass Spectrum *m/z* 442 [MH^+].
186	N-{[(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.63mins. Mass Spectrum *m/z* 440 [MH^+].
187	N-{[(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.64mins. Mass Spectrum *m/z* 460 [MH^+].
188	N-{[(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.68mins. Mass Spectrum *m/z* 458 [MH^+].
189	N-{[(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-oxazol-	Example 41	LC-MS (System A): Rt 2.50mins. Mass Spectrum *m/z* 428

	4-yl)acetamide		[MH+].
190	N-{[(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.54mins. Mass Spectrum *m/z* 426 [MH+].
191	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 2.90mins. Mass Spectrum *m/z* 492 [MH+].
192	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-phenyl-1,3-oxazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.81mins. Mass Spectrum *m/z* 460 [MH+].
193	N-cyclopropyl-3-[2-({[(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide	Example 41	LC-MS (System A): Rt 2.45 mins. Mass Spectrum *m/z* 476 [MH+].
194	3-{2-[({(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)amino]-2-oxoethyl}-N-cyclopropylbenzamide	Example 41	LC-MS (System A): Rt 2.28 mins. Mass Spectrum *m/z* 447 [MH+].
195	N-cyclopropyl-3-[2-({[(2S)-4-(4-fluorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide	Example 41	LC-MS (System A): Rt 2.11 mins. Mass Spectrum *m/z* 425 [MH+].
196	3-[2-({[(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-N-cyclopropylbenzamide	Example 41	LC-MS (System A): Rt 2.24mins. Mass Spectrum *m/z* 442 [MH+].
197	N-cyclopropyl-3-[2-({[(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide	Example 41	LC-MS (System A): Rt 2.12mins. Mass Spectrum *m/z* 444 [MH+].
198	N-cyclopropyl-3-[2-({[(2S)-4-(3,4-	Example 41	LC-MS (System A):

	dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]benzamide		Rt 2.46 mins. Mass Spectrum *m/z* 476 [MH^+].
199	N-{[(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide	Example 41	LC-MS (System A): Rt 2.90 mins. Mass Spectrum *m/z* 461 [MH^+].
200	N-{[(2S)-4-(4-fluorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide	Example 41	LC-MS (System A): Rt 2.42 mins. Mass Spectrum *m/z* 410 [MH^+].
201	N-{[(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide	Example 41	LC-MS (System A): Rt 2.57 mins. Mass Spectrum *m/z* 427 [MH^+].
202	N-{[(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide	Example 41	LC-MS (System A): Rt 2.53 mins. Mass Spectrum *m/z* 429 [MH^+].
203	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[5-methyl-2-(3-methylthien-2-yl)-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.95mins. Mass Spectrum *m/z* 494 [MH^+].
204	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(1,3-dimethyl-1H-pyrazol-5-yl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 2.63mins. Mass Spectrum *m/z* 492 [MH^+].
205	2-[2-(3-chlorothien-2-yl)-5-methyl-1,3-oxazol-4-yl]-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 41	LC-MS (System A): Rt 2.93mins. Mass Spectrum *m/z* 514,516 [MH^+].
206	N-({(2S)-4-[(5-chlorothien-2-	Example 41	LC-MS (System A):

	yl)methyl]morpholin-2-yl}methyl)-2-(5-phenyl-2H-tetraazol-2-yl)acetamide		Rt 2.69 mins. Mass Spectrum *m/z* 433 [MH$^+$].
207	N-{[(2S)-4-(3-cyanobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 2.55mins. Mass Spectrum *m/z* 449 [MH$^+$].
208	N-{[(2S)-4-(2,1,3-benzoxadiazol-5-ylmethyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 2.80mins. Mass Spectrum *m/z* 466 [MH$^+$].
209	2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]-N-{[(2S)-4-(2,3,4-trifluorobenzyl)morpholin-2-yl]methyl}acetamide	Example 54	LC-MS (System A): Rt 2.78mins. Mass Spectrum *m/z* 478 [MH$^+$].
210	2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]-N-({(2S)-4-[4-fluoro-3-(trifluoromethyl)benzyl]morpholin-2-yl}methyl)acetamide	Example 54	LC-MS (System A): Rt 2.89mins. Mass Spectrum *m/z* 510 [MH$^+$].
211	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-{5-methyl-2-[4-(methylsulfonyl)phenyl]-1,3-oxazol-4-yl}acetamide	Example 56	LC-MS (System A): Rt 2.62mins. Mass Spectrum *m/z* 552 [MH$^+$].
212	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.97mins. Mass Spectrum *m/z* 490 [MH$^+$].
213	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-pyrazin-2-yl-1,3-thiazol-4-yl)acetamide	Example 41	LC-MS (System A): Rt 2.51mins. Mass Spectrum *m/z* 492 [MH$^+$].

Example 214: N-({(2S)-4-[3-(4-chlorophenyl)propyl]morpholin-2-yl}methyl)-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide

A mixture of Intermediate 28 (0.04g), 3-(4-chlorophenyl)propanal (0.026g) and acetic acid (0.02ml) in dichloromethane (4ml) was treated with sodium triacetoxyborohydride (0.080g). The mixture was stirred at 20°C for 72h. The mixture was partitioned between chloroform (6ml) and saturated aqueous sodium hydrogen carbonate (6ml). The phases were separated and the organic phase applied to an ion exchange cartridge (2g Isolute SCX, prewashed with methanol).The SCX cartridge was eluted with methanol (10ml) followed by 10% 0.880 ammonia in methanol (10ml) and the appropriate fractions were concentrated in vacuo to give the title compound as a colourless gum (0.055g).

LCMS (system A) R_t 2.65min Mass Spectrum *m/z* 486 [MH^+].

Examples 215-219

	Name	Preparation analogous to	Characterising Data
215	2-(2-cyclopropyl-5-methyl-1,3-oxazol-4-yl)-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 158	LC-MS (System A): Rt 2.48mins. Mass Spectrum *m/z* 438 [MH^+].
216	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(2-isobutyl-5-methyl-1,3-oxazol-4-yl)acetamide	Example 158	LC-MS (System A): Rt 2.70mins. Mass Spectrum *m/z* 454 [MH^+].
217	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[5-methyl-2-(2-methylprop-1-enyl)-1,3-oxazol-4-yl]acetamide	Example 158	LC-MS (System A): Rt 2.71mins. Mass Spectrum *m/z* 452 [MH^+].
218	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-methyl-2-pyridin-2-yl-1,3-oxazol-4-yl)acetamide compound with formic acid (1:1)	Example 158	LC-MS (System A): Rt 2.38mins. Mass Spectrum *m/z* 475 [MH^+].
219	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[5-(4-fluorophenyl)-2H-tetraazol-2-yl]acetamide	Example 41	LC-MS (System A): Rt 2.85 mins. Mass Spectrum *m/z* 479 [MH^+].

Example 220: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]acetamide

A mixture of Intermediate 38 (0.024g), Intermediate 9(0.025g), and 1-methyl-2-pyrrolidinone (1 drop) was subjected was subjected to irradiation in a 600W microwave oven on full power for 4 mins. The reaction mixture was dissolved in methanol and applied to an ion exchange cartridge (2g Isolute SCX, pre-conditioned with methanol). Elution with methanol (3 column volumes) followed 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the first basic fraction in vacuo gave the crude product. Purification by Biotage flash column chromatography on silica gel (8g cartridge), eluting with 100:8:1 dichloromethane/ethanol/0.880 ammonia, gave the title compound as a white solid (0.025g).

LCMS (System A) R_t 2.85min Mass Spectrum *m/z* 479, 481 [MH^+]

Examples 221-224

	Name	Preparation analogous to	Characterising Data
221	N-{[(2S)-4-(2,1,3-benzothiadiazol-5-ylmethyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 2.51mins. Mass Spectrum *m/z* 482 [MH^+].
222	4-{4-[2-({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-2-oxoethyl]-5-methyl-1,3-oxazol-2-yl}-N,N-dimethylbenzamide	Example 56	LC-MS (System A): Rt 2.50mins. Mass Spectrum *m/z* 545 [MH^+].
223	2-{2-[4-(acetylamino)phenyl]-5-methyl-1,3-oxazol-4-yl}-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide	Example 56	LC-MS (System A): Rt 2.54mins. Mass Spectrum *m/z* 531 [MH^+].
224	N-{[(2S)-4-(1,2,3-benzothiadiazol-6-ylmethyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 214	LC-MS (System A): Rt 2.59mins. Mass Spectrum *m/z* 482 [MH^+].

Example 225: N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}pentanamide

A solution of Intermediate 9 (0.028g) in dichloromethane (2ml) containing a suspension of polyvinyl pyridine (0.1g) was treated with valeryl chloride (0.018ml), and the mixture was

shaken at 20°C for 16h. Tris (2-aminoethyl)amine polystyrene scavenger resin (Argonaut Technologies, 4.46mmol/g; 0.067g) was added, and the mixture was shaken at 20°C for 2h. The mixture was filtered and the filtrate applied directly to a silica gel cartridge (1g Varian Bond Elut). Elution with chloroform, ether, and ethyl acetate gave the title compound (0.0225g).

LC-MS (System A) Rt 2.43mins. Mass Spectrum *m/z* 359 [MH^+].

Examples 226-238

	Name	Preparation analogous to	Characterising Data
226	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-4-methylpentanamide	Example 225	LC-MS (System A): Rt 2.58mins. Mass Spectrum *m/z* 373 [MH^+].
227	N-({4-[3-(3,4-dichlorophenyl)propyl]morpholin-2-yl}methyl)-2-phenoxyacetamide	Example 1	LC-MS (System A): Rt 2.76 mins. Mass Spectrum *m/z* 437 [MH^+].
228	2-cyclohexyl-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide trifluoroacetate	Example 1	LC-MS (System A): Rt 2.81mins. Mass Spectrum *m/z* 399 [MH^+].
229	2-(4-chlorophenyl)-N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}propanamide	Example 1	LC-MS (System A): Rt 3.00mins. Mass Spectrum *m/z* 443 [MH^+].
230	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(1,1-dioxidothiomorpholin-4-yl)acetamide	Example 1	LC-MS (System A): Rt 2.39mins. Mass Spectrum *m/z* 450 [MH^+].
231	2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]-N-({(2S)-4-[2-(4-fluorophenyl)-2-oxoethyl]morpholin-2-	Example 54	LC-MS (System A): Rt 2.58mins. Mass Spectrum *m/z* 470 [MH^+].

	yl}methyl)acetamide		
232	N-({(2S)-4-[(3-chloro-1-benzothien-2-yl)methyl]morpholin-2-yl}methyl)-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 3.46mins. Mass Spectrum *m/z* 514 [MH^+].
233	2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]-N-{[(2S)-4-(2-methylprop-2-enyl)morpholin-2-yl]methyl}acetamide	Example 54	LC-MS (System A): Rt 2.37mins. Mass Spectrum *m/z* 488 [MH^+].
234	2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]-N-{[(2S)-4-(1-phenylethyl)morpholin-2-yl]methyl}acetamide	Example 54	LC-MS (System A): Rt 2.48mins. Mass Spectrum *m/z* 438 [MH^+].
235	N-{[(2S)-4-(3-cyano-4-fluorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 2.59mins. Mass Spectrum *m/z* 467 [MH^+].
236	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-isopropyl-1,3-oxazol-4-yl]acetamide	Example 41	LC-MS (System A): Rt 3.16 mins. Mass Spectrum *m/z* 520 [MH^+].
237	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}cyclopropane carboxamide	Example 225	LC-MS (System A): Rt 2.22mins. Mass Spectrum *m/z* 343 [MH^+].
238	N-({(2S)-4-[2-(3-chlorophenoxy)ethyl]morpholin-2-yl}methyl)-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide	Example 54	LC-MS (System A): Rt 2.72mins. Mass Spectrum *m/z* 488 [MH^+].

Example 239: N-{[(2S)-4-(3,4-dichlorobenzoyl)morpholin-2-yl]methyl}-2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]acetamide

A mixture of Intermediate 12 (0.015g), 1-hydroxybenzotriazole (0.0097g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.012g) and N,N-

diisopropylethylamine (0.027ml) in N,N-dimethylformamide (2ml) was stirred at 20°C for 10min. The mixture was treated with Intermediate 31 (0.023g) and stirred at 20°C for 96h. The mixture was applied sequentially to a sulphonic acid ion exchange cartridge (1g SCX, prewashed with methanol) and Isolute^{R} aminopropyl solid phase extraction cartridge (1g), eluting both cartridges with methanol (5ml). The solvent was removed in vacuo to give the title compound as a yellow gum (0.032g).

LCMS (system A) R_t 3.3min Mass Spectrum *m/z* 506 [MH^+]

Example 240: tert-butyl 4-[3-({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)-3-oxopropyl]piperidine-1-carboxylate

Example 240 was prepared in an analogous manner to Example 44 from 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]propanoic acid.

LC-MS (System A) Rt 2.89mins Mass Spectrum *m/z* 514 [MH^+]

Biological Data

The compounds of the Examples were tested in the CCR-3 binding and/or eosinophil chemotaxis assays (assays (a) and (b)) and results were obtained as follows:

Example	CCR-3 Binding Assay (pIC50)	CCR-3 Eosinophil Chemotaxis Assay (fpKi)
2		6.51
3		7.15
5	7.11	
6	6.86	
7	7.82	
8	6.84	
10	6.80	
12		6.82
13	6.62	
14	6.47	
17		6.24
19	6.08	
22	6.96	
25	7.22	
27		7.39
31	6.29	

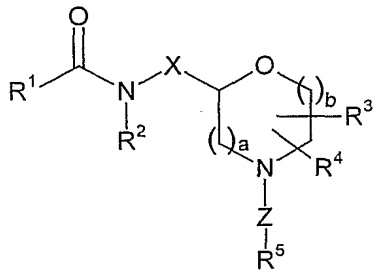
32		7.32
35	6.81	
37		7.97
38	7.00	
39		8.31
41		7.99
42		9.32
44	8.17	
45	7.88	
46	7.14	
49		8.07
53	8.39	
54	7.62	7.96
55	6.40	
162	7.9	8.2

Compounds of Examples 1, 4, 9, 11, 15-16, 18, 20-21, 23-24, 26, 28-30, 33-34, 36, 40, 43, 47-48, 50-52, 56-161 and 163-240 were also tested in CCR-3 binding assay (assay (a)) and achieved a pIC50 value greater than 5.0.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkynyl-Y^1-, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^2-Y^1-, -CN or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl;

X represents ethylene or a group of formula CR^eR^f wherein R^e and R^f independently represent hydrogen or C_{1-4} alkyl or R^e and R^f may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^3 and R^4 independently represent hydrogen or C_{1-4} alkyl;

Z represents a bond, CO, SO_2, $CR^9R^6(CH_2)_n$, $(CH_2)_nCR^9R^6$, $CHR^6(CH_2)_nO$, $CHR^6(CH_2)_nS$, $CHR^6(CH_2)_nOCO$, $CHR^6(CH_2)_nCO$, $COCHR^6(CH_2)_n$ or $SO_2CHR^6(CH_2)_n$;

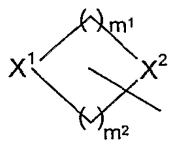
R^5 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl-C_{2-6} alkenyl- or a group of formula $-Y^2$-J^1;

R^6 represents hydrogen, C_{1-4} alkyl, $CONR^7R^8$ or $COOC_{1-6}$ alkyl;

a and b represent 1 or 2, such that a+b represents 2 or 3;

n represents an integer from 0 to 4;

J^1 and J^2 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{13} or sulphur, X^2 represents CH_2, oxygen, NR^{10} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{13}, NR^{10} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-COC_{3-8}$cycloalkyl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3$-$COOC_{1-6}$ alkyl, $-Y^3$-COC_{1-6} alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3$-$NR^{11}R^{12}$, $-Y^3$-$CONR^{11}R^{12}$, hydroxy, oxo, $-Y^3$-$SO_2NR^{11}R^{12}$, $-Y^3$-SO_2C_{1-6} alkyl, $-Y^3$-SO_2aryl, $-Y^3$-SO_2heteroaryl, $-Y^3$-$NR^{14}C_{1-6}$ alkyl, $-Y^3$-$NR^{14}SO_2C_{1-6}$ alkyl, $-Y^3$-$NR^{14}CONR^{11}R^{12}$, $-Y^3$-$NR^{14}COOR^{15}$ or $-Y^3$-$OCONR^{11}R^{12}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14} and R^{15} independently represent hydrogen or C_{1-6} alkyl;

R^{11} and R^{12} independently represent hydrogen or C_{1-6} alkyl or R^{11} and R^{12} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

M represents a C_{3-8} cycloalkyl or a C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-6} alkyl, halogen or hydroxy groups;

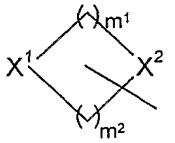
t represents 0 or 1.

Y^1, Y^2 and Y^3 independently represent a bond or a group of formula $-(CH_2)_pCR^cR^d(CH_2)_q-$ wherein R^c and R^d independently represent hydrogen or C_{1-4} alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5;

and salts and solvates thereof.

2. A compound of formula (I) according to claim 1 wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkynyl-Y^1-, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups; and

J^1 represents a moiety of formula (K):



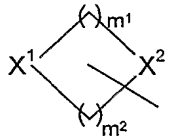
(K)

wherein X^1 represents oxygen, NR^{13} or sulphur, X^2 represents CH_2, oxygen, NR^{10} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{13}, NR^{10} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{11}R^{12}$, $-Y^3-CONR^{11}R^{12}$, hydroxy, oxo, $-Y^3-SO_2NR^{11}R^{12}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{14}C_{1-6}$ alkyl, $-Y^3-NR^{14}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{14}CONR^{11}R^{12}$, $-Y^3-NR^{14}COOR^{15}$ or $-Y^3-OCONR^{11}R^{12}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

3. A compound of formula (I) according to claim 1 wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

Z represents a bond, CO, $CR^9R^6(CH_2)_n$, $CHR^6(CH_2)_nO$, $CHR^6(CH_2)_nS$, $CHR^6(CH_2)_nOCO$, $CHR^6(CH_2)_nCO$; and

J^1 represents a moiety of formula (K):



(K)

wherein X^1 represents oxygen, nitrogen, NR^{13} or sulphur, X^2 represents CH_2, oxygen, nitrogen, NR^{10} or sulphur, m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when X^2 represents oxygen, nitrogen, NR^{10} or sulphur, $m^1$and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{11}R^{12}$, $-Y^3-CONR^{11}R^{12}$, hydroxy, oxo, $-Y^3-SO_2NR^{11}R^{12}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{14}C_{1-6}$ alkyl, $-Y^3-NR^{14}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{14}CONR^{11}R^{12}$, $-Y^3-$

$NR^{14}COOR^{15}$ or $-Y^3-OCONR^{11}R^{12}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

4. A compound of formula (I) according to any one of claims 1 to 3 wherein R^1 represents aryl-Y^1-.

5. A compound of formula (I) according to claim 4 wherein R^1 represents optionally substituted phenyl-Y^1- in which phenyl may be optionally substituted.

6. A compound of formula (I) according to any one of claims 1 to 5 wherein Y^1 represents $-CH_2-$.

7. A compound of formula (I) according to claim 1 wherein X represents methylene.

8. A compound of formula (I) according to claim 1 wherein a and b both represent 1.

9. A compound of formula (I) according to claim 1 or claim 3 wherein Z represents a bond, CO, $CHR^6(CH_2)_n$, $CHR^6(CH_2)_nO$ or $CHR^6(CH_2)_nCO$.

10. A compound of formula (I) according to claim 9 wherein Z represents CH_2.

11. A compound of formula (I) according to claim 1 wherein R^6 represents phenyl optionally substituted with one or more halogen atoms.

12. A compound of formula (I) according to claim 11 wherein R^6 represents 3,4-dichlorophenyl.

13. A compound of formula (I) according to any one of claims 1 to 12 as described in Examples 1 to 240 or a salt or solvate of any one thereof.

14. A compound of formula (I) according to claim 13 which is 2-[3-(Aminosulfonyl)phenyl]-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide or a solvate thereof.

15. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

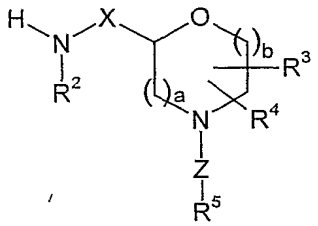
16. A compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

17. Use of a compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of inflammatory diseases.

18. A method of treatment or prophylaxis of inflammatory diseases eg. asthma which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof.

19. A process for preparing a compound of formula (I) according to any one of claims 1 to 14 which comprises:

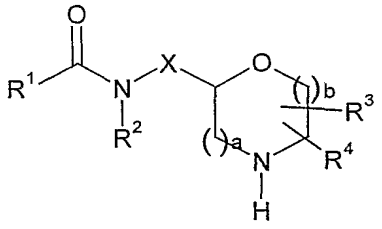
(a) acylation of a compound of formula (II)



(II)

wherein R^2, R^3, R^4, R^5, X, Z, a and b are as defined in claim 1, with a compound of formula R^1COOH or an activated derivative thereof, wherein R^1 is as defined in claim 1; or

(b) reacting a compound of formula (III)



(III)

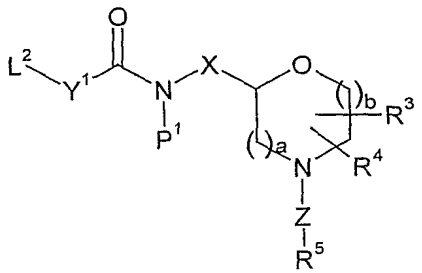
wherein R^1, R^2, R^3, R^4, X, a and b are as defined in claim 1, with a compound of formula L^1-Z-R^5, wherein Z and R^5 are as defined in claim 1 and L^1 represents a suitable leaving group; or

(c) deprotecting a compound of formula (I) which is protected; or

(d) interconversion of other compounds of formula (I).

20. A process for preparing a compound of formula (I) according to any one of claims 1 to 14 which comprises:

(e) forming a compound of formula (I) wherein R^1 represents heteroaryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1- or heteroaryl-$(O)_t$-heteroaryl-Y^1- (wherein said Y^1 group is attached to heteroaryl via a heterocyclic nitrogen atom) and R^2 represents hydrogen which comprises reacting a compound of formula (IV)



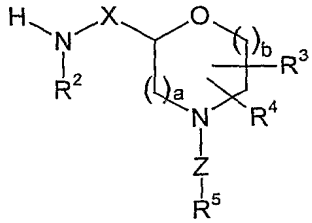
(IV)

or a protected derivative thereof wherein R^3, R^4, R^5, X, Y^1, Z, a and b are as defined in claim 1, L^2 represents a suitable leaving group, such as a halogen atom eg. bromine and P^1 represents a solid phase resin bound protecting group, with a heterocyclic compound defined by the R^1 groups heteroaryl, aryl-$(O)_t$-heteroaryl or heteroaryl-$(O)_t$-heteroaryl above wherein said heteroaryl group contains at least one NH atom, followed by removal of the solid phase resin bound protecting group; or

(f) forming a compound of formula (I) wherein Z represents $CR^9R^6(CH_2)_n$ and R^9 represents hydrogen which comprises reacting a compound of formula (III) or a protected derivative thereof with a compound of formula $R^6CO(CH_2)_nR^5$, followed by reduction of the resultant imine; or

(g) forming a compound of formula (I) wherein Z represents CO by reacting a compound of formula (III) or a protected derivative thereof with a compound of formula R^5COOH or an activated derivative thereof.

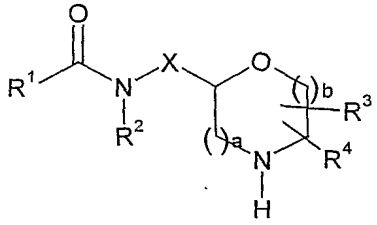
21. A compound of formula (II)



(II)

wherein R^2, R^3, R^4, R^5, X, Z, a and b are as defined in claim 1 or a protected derivative thereof, or a salt or solvate thereof.

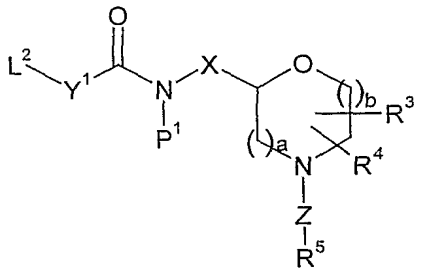
22. A compound of formula (III)



(III)

wherein R^1, R^2, R^3, R^4, X, a and b are as defined in claim 1 or a protected derivative thereof, or a salt or solvate thereof.

23. A compound of formula (IV)



(IV)

wherein R^3, R^4, R^5, X, Y^1, Z, a and b are as defined in claim 1, L^2 represents a suitable leaving group, such as a halogen atom eg. bromine and P^1 represents a solid phase resin bound protecting group, or a salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB 01/04345

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D265/30 C07D413/12 C07D417/12 C07D413/06 C07D417/14
C07D413/14 A61K31/5375 A61K31/5377 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 243 959 A (DAINIPPON PHARMACEUTICAL CO) 4 November 1987 (1987-11-04) claims ---	1-3,15, 19
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2001	10/01/2002

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte ıl Application No
PCT/GB 01/04345

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	S. KATO ET AL.: "Novel benzamides as selective and potent gastrokinitic agents." CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 40, no. 3, 1992, pages 652-660, XP002012408 PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO., JP ISSN: 0009-2363 the whole document	1-23
A	S. KATO ET AL.: "Novel benzamides as selective and gastrokinetic agents" JOURNAL OF MEDICINAL CHEMISTRY., vol. 34, no. 2, 1991, pages 616-624, XP002185243 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document	1-23
P,X	WO 00 71518 A (SEPRACOR INC) 30 November 2000 (2000-11-30) claims; examples	1,15,19

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Information on patent family members

Inte al Application No
PCT/GB 01/04345

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